Pharmacosurveillance for SJS/TEN in the US

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Outline

- List Tools currently in use at FDA
- Describe each tool in terms of
  - Characteristics & Uses
  - Strengths
  - Limitations

- Summarize & identify gaps in PS
- Suggestions for possible improvement

Pharmacosurveillance (PS) Tools Used by FDA

- Pharmacovigilance (PV)
  - FDA Adverse Event Reporting system (FAERS)
    - (Data mining)
  - Medical Literature (PubMed Alerts)
  - VigiBase

PS Tools – Pharmacoepidemiology (PE)

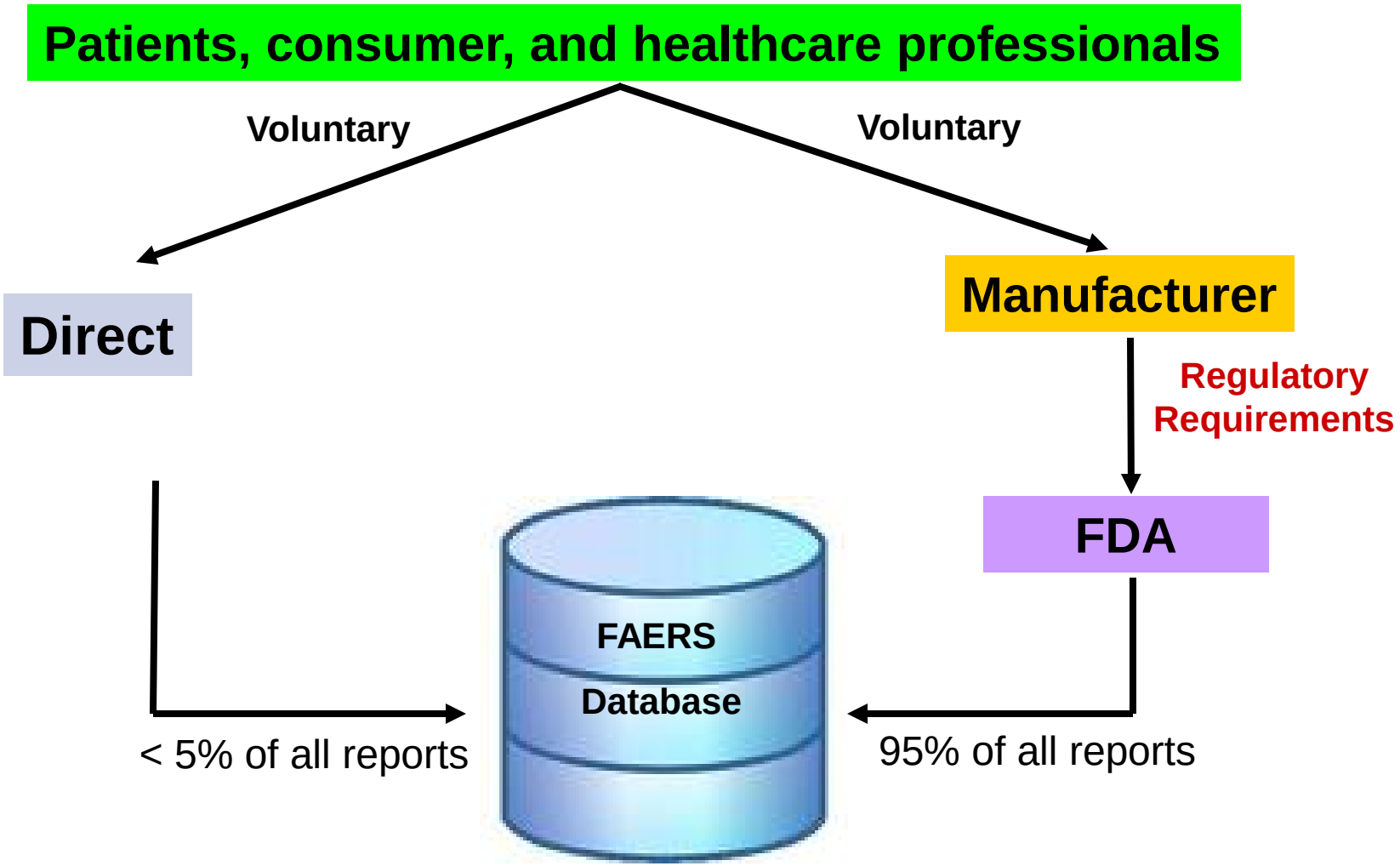
- National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance (NEISS-CADES)
- PE (Database) studies
- Sentinel / Mini-sentinel

FAERS

PV - FAERS

- Computerized database
- Spontaneous adverse event reports
- Associated with human and therapeutic biologic drug products
- > 10 million reports since 1969
- ~ 1 million new reports in 2013 & 2014

Sources of FAERS Reports



Adapted from OSE archived slide presentations

FAERS Strengths

- Simple, relatively inexpensive
- Very good for detecting rare AEs with short latency period (e.g. SJS/TEN) that are difficult to detect in clinical trials
- Inclusive
  - All ages & populations
  - All marketed drugs & biologics in US

Limitations

- Underreporting (cannot be used for incidence; no denominator)
- Information not always complete
- Reporting varies over time and with other activities
  - e.g. publicity, litigation

Proportion of SJS TEN Reports in FAERS 2010 - 2014

- Jan 2010 – December 2014
- Total FAERS reports – 4,734,000
- Total SJS/TEN reports – 5, 700
- 0.12%

Signal Detection for SJS/TEN

- Regular review of FAERS – daily / weekly alerts
- (Data mining- Empirica software)
- Medical literature alerts
- Information from other Regulatory authorities
- VigiBase

Sample1, FAERS SJS/TEN report

- Reporter: Nurse practioner via sales rep.
- Female patient, unknown age , developed SJS on unknown date while on Drug A
- Concomitant meds, comorbidities unknown
- Outcome unknown
- Follow-up not successful

Sample 2, SJS/TEN FAERS report

- M, 52 yo on drug X for diabetes
- Not well controlled after 9 months
- Drug Y added
- 13 days later – generalized erythematous rash, bilateral conjunctival hyperemia
- Visited dermatologist, diagnosis SJS, hospitalized, all drugs discontinued, treated with systemic steroids, ophthalmology consultation
- Discharged after 1 month – all symptoms resolved

SJS/TEN diagnostic Criteria for FAERS cases

- Diagnosis likely:
  - Diagnosis made by dermatologist
  - Good clinical description, with record of % BSA affected
  - ICU or Burn unit admission
  - Biopsy confirmation
- Less likely, still possible
  - Diagnosed by non dermatologist, no supporting information

Causality Criteria – modified WHO-UMC

- Probable:
  - Reasonable temporal association
  - Absence of confounding factors
  - Positive dechallenge +/- positive rechallenge
- Possible:
  - Reasonable temporal association
  - Confounded – alternative causes possible

Comparison with ALDEN causality scoring system

- Similar elements considered e.g. reasonable temporal association, dechallenge, rechallenge, alternative causes etc.

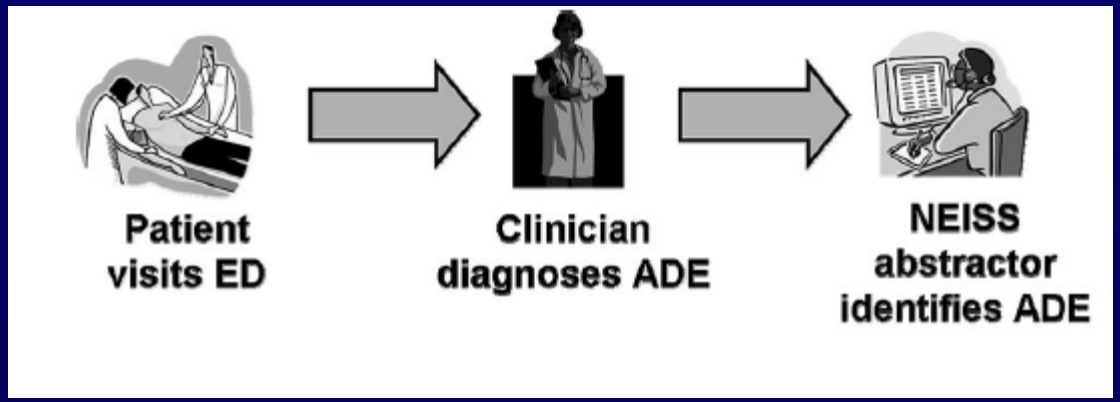
- Different in that ALDEN more detailed
  - ascribes a particular score
  - one element requires prior knowledge of the drug - often assessing new drugs at FDA

NEISS-CADES

NEISS-CADES

- Collaboration of CPSC, CDC, and FDA
  - Active surveillance for adverse drug events (ADEs) treated in Emergency Departments (EDs)
- National Probability sample of ~ 60 US hospitals
  - With a minimum of 6 beds and a 24-hour ED
  - Excludes psychiatric and penal institutions
- ADE: an ED visit for a condition that the treating clinician explicitly attributes to therapeutic use of a drug or drug product

NEISS-CADES Data Collection Process



Data transferred to CPSC

Additional coding and data validation (including assignment of MedDRA codes)

Adapted from: Jhung MA, Budnitz DS, Mendelsohn AB, Weidenbach KN, Nelson TD, Pollock DA. Med Care. 2007 Oct;45(10 Supl 2):S96-102; CPSC = Consumer Product Safety Commission

Case Detail - (Update Mode) *[Source Jhung MA et al, Med Care. 2007 Oct;45(10 Supl 2):S96-102].*

NEISS Case | Adverse Drug Event

Did an adverse drug event occur? Adverse Drug events:
INCLUDE side-effects, allergic reactions and medication errors.
INCLUDE accidental ingestions in children and unintended overdosage or high levels of medication in adults.
Do NOT report drug abuse, 'recreational' drug use, self-harm or cases due to alcohol or illegal drugs.
Drugs include: Prescription Medications, Over-the-Counter Medications, Medicated Creams/Ointments, Vaccinations/Immunizations, Vitamins, and Herbal/Nutritional Supplements [Yes]

What was the primary reason the patient came to the ED?

Record the following information about the drug linked to the adverse event (up to 2 drugs can be listed).

	Drug #1	Drug #2
What was the name of the drug? If no information, type "Unknown"		
How much was taken at a time? If a pill, list milligrams and number of pills. If other dosing information is reported, record this in the box below Please specify:	.000 mg pills	.000 mg pills
How many times a day did the patient take the drug?		
How did the patient take the drug?		
How long has the patient been taking the drug? Enter a number then choose the time period.		

What was the final diagnosis (Dx) or clinical impression?

What treatments were given in the ED?

If any special lab tests were ordered for the adverse drug event, which ones and what were the results?

Please record any other information describing the event

If the patient was taking other drugs, what were the names of these drugs? (May list up to 10)

SJS/TEN Case Definition MedDRA terms

SOC *(System Organ Class):*

Skin and subcutaneous tissue disorders

HLGT *(High Level Group Term):*

Epidermal and dermal conditions

HLT *(High level term):*

Bullous conditions

PT *(Preferred Term*):

Erythema multiforme, Stevens Johnson syndrome, or Toxic Epidermal Necrolysis

NEISS-CADES - Strengths

- Nationally representative, so can be used to calculate incidence rates
- Can also be used as an additional source of cases in PV to supplement FAERS
- Diagnosis made by ED clinician, so better than ICD codes

NEISS-CADES - Limitations

- Diagnosis not confirmed by dermatologist / biopsy (use hospitalized cases to ↓ misdiagnosis)
- Lag time of ~15 months for database to be updated
- Does not capture:
  - SJS/TEN not caused by drugs
  - cases in hospitalized patients
  - cases dying on way to ED

Pharmacoepidemiology (PE) Studies

PE studies in PS for SJS/TEN

- Prospective data collection; *e.g.* registries
  - Challenging in the U.S. because of fragmented healthcare system
  - Large number of enrolled patients is needed

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PE studies *cont.*

- Retrospective studies; *e.g.* administrative databases
  - *Strengths:* real world settings, potentially large number of patients with longitudinal follow-up
  - *Main limitation*: SJS/TEN cases poorly captured by administrative codes (medical record validation needed)

Sentinel

Sentinel

- Launched in 2008 by FDA; pilot program Mini-Sentinel
- Active surveillance system for monitoring safety of marketed FDA regulated products
  - complements other safety surveillance systems
- PE - based on electronic health records – electronic medical records, administrative claims data, registries
- Pre-specified modular programs developed, ready for implementation so can be completed quickly

Sentinel

- Transition to Sentinel now in progress
- Awarded to Harvard Pilgrim Healthcare Institute
- 50+ healthcare and academic organizations
- Current total – 180 million covered lives
  - ~ 50 million /year in last 5 years
- Limitations: SJS/TEN ICD codes do not have high PPV

Summary

- FAERS – Main PV tool for SJS/TEN
- NEISS-CADES useful, but more could be done as more data accumulate
- PE studies limited by poor validation of ICD codes
- Sentinel – not yet useful
- MASE – still under development

Suggestions for improvement in PV in US

- Targeted active surveillance
  - ICU & burn units
- Follow-up of cases identified in NEISS-CADES
  - Confirmation of diagnosis
  - Treatment
  - Length of stay
  - Mortality & associated risk factors
- Network of dermatologists – based on DILIN model – DISIN? DISCARN?

Acknowledgements

- All colleagues in Office of Surveillance & Epidemiology
- Especially the Divisions of Pharmacovigilance I & II

Back Up Slides

Molecular Analysis of Side Effects (MASE)

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FDA contact: Keith Burkhart

MASE

- MASE integrates the publicly available FAERS data with chemical and biological data sources: DrugBank, PubChem, UniProt, NCI Nature, Reactome, BioCarta, and PubMed.

- Mechanistically evaluate an adverse event by highlighting molecular targets, enzymes and transporters that may be disproportionately associated with an AE.

MASE - Limitations

- Research Hypothesis Generation Tool
- Uses PRR as a disproportionality analysis tool
- 5-Year RCA (Research Collaboration Agreement) with Molecular Health