

**ACTIVE Surveillance to improve
the VALUE of Pharmacovigilance
as a Public Health tool**

**THINK TANK,
Rockville MD**

5/22-23 2007

**ACTIVE Surveillance to improve
the VALUE of Pharmacovigilance
as a Public Health tool**

KEY LEARNINGS
FROM DAY ONE
OF THE THINK
TANK

KEY LEARNINGS FROM DAY ONE

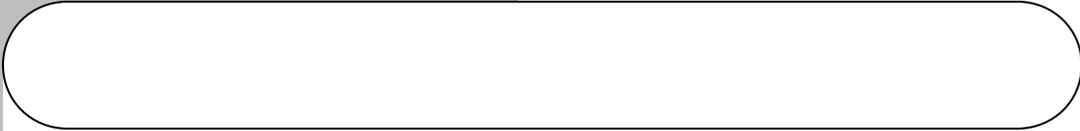
- THE POTENTIAL GAIN FROM CREATION OF A HIGHLY COORDINATED NETWORK OF POPULATION-BASED DATA BASES (SUPPLEMENTED WITH DATA FROM REGISTRIES AND RCTs AND OTHER STUDIES) WILL BE GREAT AND IS WITHIN OUR REACH
- A SINGLE LARGE COMBINED DATABASE IS NOT THE RIGHT OBJECTIVE

KEY LEARNINGS FROM DAY ONE

- A CONTINUUM APPROACH TO EVOLVING CUMULATIVE DATA (MARGINAL RISK) IS SUPERIOR TO THE NOW OUTMODED NOTION OF "SIGNALS" FROM ANECDOTES
- WHEN YOU MONITOR A SUBSTANTIAL PROPORTION OF THE POPULATION ISSUES SUCH AS DATA QUALITY AND CLINICAL PRACTICE PATTERNS ARE MORE IMPORTANT THAN ESTIMATES OF VARIATION ATTRIBUTABLE TO SAMPLING
- THE DATA FROM SUCH LARGE POPULATIONS CAN INFORM ON THE TRUE PUBLIC HEALTH IMPACT

KEY LEARNINGS FROM DAY ONE

- A SET OF STANDARD OPERATING PROCEDURES ABOUT HOW TO THINK AND COMMUNICATE ABOUT EXCESS RISK IS POSSIBLE AND DESIRABLE
- A 'QUICK WIN' IS NEEDED THAT PEOPLE WILL CARE ABOUT... AND SOON... FROM THESE LINKED DATA BASES, E.G. MONITORING FOR A RARE SERIOUS EVENT (E.G., STEVENS JOHNSON SYNDROME), ALL CASES OF WHICH CAN BE CONFIRMED BY MEDICAL RECORD REVIEW, OR A COMMON SERIOUS EVENT (E.G., ACUTE MI,) WHICH DOES NOT NEED REVIEW FOR ROUTINE MONITORING PURPOSES



KEY LEARNINGS FROM DAY ONE



- **A CONSORTIUM WILL BE NEEDED TO
MANAGE AND LEAD THESE EFFORTS**

The CERTs Risk Series Methods

“the TICKET to dinner”

- **Listened yesterday for important changes that need to be made and nominated the most important for each of 3 areas**
 - Identification of anticipated signals
 - Identification of unanticipated signals
 - Signal evaluation
- **Moderators/reporters identified key themes and potential efforts based on responses**
- **Foundation for breakout discussions today**

DAY TWO:

Where are the key opportunities?

- What are the **THREE** most important changes to improve the national capacity to identify or evaluate signals within the next **FIVE** years ?
- What are the **THREE** most important efforts/initiatives to implement the changes within the next **TWO** years?
- What are the most feasible and useful **NEXT STEPS?**

Opportunities for Active Surveillance to improve the Value of Pharmacovigilance as a Public Health Tool

... with apologies for any errors in
interpretation, transcription,
abbreviation ... etc!!



Opportunities for Active Surveillance to improve the Value of Pharmacovigilance as a Public Health Tool

... with thanks for the great help
from the panel leaders and Rich,
Jim, and Leanne!!



DAY TWO:

ANTICIPATED SIGNALS: What are the key long term CHANGES

- BUILD AND SUSTAIN A TEAM/PUBLIC PRIVATE PARTNERSHIP/MULTI-AGENCY INVOLVEMENT (transparency, advisory functions re next steps with signals, priorities)
- ACCESS TO MERGED, LINKED, AGGREGATED, DISTRIBUTED DATA FROM MULTIPLE SOURCES INCLUDING PART “D”
- DEVELOP, VALIDATE, AND STANDARDIZE ANALYTIC METHODS (including datamining and active surveillance)

DAY TWO:

ANTICIPATED SIGNALS: What are the key long term CHANGES (cont'd)

- STANDARDIZE CODING, TERMINOLOGY, DICTIONARIES
- USE RCT AND PHASE IV (post-marketing) DATA TO IDENTIFY “ANTICIPATED” SIGNALS (public/transparent; improve quality)
- ... AND MANY OTHER GREAT IDEAS!

DAY TWO:

ANTICIPATED SIGNALS: What are the key efforts/initiatives in the next two years: BUILD A SUSTAINABLE TEAM

- **PRIORITIZE AND FUND 'QUICK WINS'**
- **SUBSET OF THIS TEAM FOR A DEEPER EXAMINATION OF KEY ... MEASURES OF SUCCESS**
- **DISCUSS WITH DISEASE-ORIENTED GROUPS**
- **PREDICTABLE, SUSTAINABLE BUSINESS MODELS**

DAY TWO:

ANTICIPATED SIGNALS: What are the key efforts/initiatives in the next two years: BUILD A SUSTAINABLE TEAM

- IDENTIFY CANDIDATES THAT SHARE/COULD SHARE DATA
- CLARIFY THE PROCESS FOR PUBLIC PRIVATE PARTNERSHIPS ... GAIN INDUSTRY BUY-IN AND SUPPORT
- COMPILE AND DISSEMINATE “HOT TOPICS”
- DEVELOP A PRIORITIZATION MECHANISM
- GOVERNMENT ISSUE RFP’s FOR THE TEAM

DAY TWO:

ANTICIPATED SIGNALS: What are the key efforts/initiatives in the next two years: BUILD A SUSTAINABLE TEAM

- DEVELOP COMMON DATA STRUCTURE
- DEVELOP COMPARABILITY AND COMPATABILITY OF THE DATA SETS
- DEVELOP PUBLIC PRIVATE ADVISORY GROUP TO MAKE RECOMMENDATIONS ON HOW TO “MANAGE” THE SIGNALS WITH FURTHER STUDY, PRIORITY SETTING, RISK COMMUNICATION

ANTICIPATED SIGNALS: What are the key efforts/initiatives in the next two years: ACCESS TO MERGED ... DATA FROM MULTIPLE SOURCES

- **FEDERAL FACILITATION/INCENTIVES**
- **ESTABLISH DISEASE REGISTRIES**
- **RE-WORK HIPAA AND CONFIDENTIALITY ISSUES**
- **INCREASE CERTS FUNDING FOR SAFETY**

ANTICIPATED SIGNALS: What are the key efforts/initiatives in the next two years: ACCESS TO MERGED ... DATA FROM MULTIPLE SOURCES

- EXTEND THE CURRENT DeCIDE RFA/CONTRACT; PDUFA IV FUNDING
- GET CMS ON BOARD
- CREATE A NATIONAL 'EXPERT GROUP' ON COORDINATED RESOURCES
- GAIN AGREEMENT AMONG THE HOLDERS OF THE INDIVIDUAL DATA SETS

ANTICIPATED SIGNALS: What are the key efforts/initiatives in the next two years: ACCESS TO MERGED ... DATA FROM MULTIPLE SOURCES

- DO A PILOT STUDY
- SHARE DATA AND RESULTS AND TOOLS
- STUDY/DOCUMENT COSTS
- ROUTINE POST APPROVAL STUDIES AND DATABASE SCREENING FOR MAIN EVENTS OF INTEREST

ANTICIPATED SIGNALS: What are the key efforts/initiatives in the next two years: ACCESS TO MERGED ... DATA FROM MULTIPLE SOURCES

- GREATER LINKAGE OF EMR AND CLAIMS DATA
- METHODS WORKSHOP
- DESIGNATED CENTERS OF EXCELLENCE
- NEED THE APPROPRIATE H.I.T. TOOLS
- INCENTIVES
- CONGRESSIONAL MANDATE/PDUFA

ANTICIPATED SIGNALS: What are the key efforts/initiatives in the next two years: DEVELOP, VALIDATE, STANDARDIZE ANALYTIC METHODS

- CRITERIA/"TRIGGERS" FOR "ANTICIPATED EVENTS"
- RFA FOR METHODS/ AHRQ TAKES THIS ON
- PROVIDE TRAINING FOR DATABASE EXPERTS/ CONGRESS APPROPRIATES FOR EPIDEMIOLOGIST TRAINING

ANTICIPATED SIGNALS: What are the key efforts/initiatives in the next two years: DEVELOP, VALIDATE, STANDARDIZE ANALYTIC METHODS

- R&D INTO DISEASE-EXPECTED EFFECTS
- LIBRARY OF METHODS
- ROLE OF HUMAN-EXPERT VERSUS THE COMPUTER FOR SIGNAL DETECTION AND TRIAGE ...THE “BRAIN BETWEEN THE NUMBERS”
- SYSTEMATIC FOLLOWUP WITHIN THE DATA NETWORKS OF ALL NEW DRUGS

ANTICIPATED SIGNALS: What are the key efforts/initiatives in the next two years: STANDARDIZE CODING, TERMINOLOGY, DICTIONARIES

- CONSENSUS (BY AHIC MEMBERS AND LEADERSHIP)
- BUILD REPOSITORY OF AGREED CONVENTIONS AND APPROACHES
- COMMITMENT TO THESE FROM STAKEHOLDERS, ESP CMS

ANTICIPATED SIGNALS: What are the key efforts/initiatives in the next two years:RCTs

- MAKE THE RESULTS OF RCTs PUBLIC
- INCENTIVIZE EXTENSION OF PATENT LIFE
- COMBINED NATIONAL PLACEBO DATABASE
- “CONTINGENT APPROVAL”

DAY TWO:

ANTICIPATED SIGNALS: What are the most feasible and useful next steps?

- GET TO WORK, FOLKS!! THIS IS TODAY'S DELIVERABLE.

DAY TWO:

UN-ANTICIPATED SIGNALS: What are the key long term CHANGES

- BIG DATA NETWORK STARTING WITH FEDERAL DATABASES ... MEDICARE PART D, DoD, VA WITH LINKAGES TO OTHER DATA INCLUDING PATIENT SURVEYS AND EMR WHERE POSSIBLE (... HMMMM ... DOES THIS LOOK FAMILIAR?)

DAY TWO:

UN-ANTICIPATED SIGNALS: What are the key long term CHANGES

- INCREASE EDUCATIONAL FUNDING
- FDA LEADERSHIP
- PUBLIC EDUCATION AND PUBLIC ENGAGEMENT TO GET CONGRESSIONAL APPROPRIATION TO FDA AND OTHER ENTITIES
- DATA STANDARDS, DATA QUALITY, SIZE OF THE DATA BASE, PRIORITIZATION OF METRICS FOR MEASURING SUCCESS

DAY TWO:

UN-ANTICIPATED SIGNALS: What are the key long term CHANGES

- VALIDATION OF SIGNAL DETECTION STATISTICAL METHODS DEVELOPMENT FOR SIGNAL DETECTION, SEQUENTIAL ANALYSIS METHODS TO MINIMIZE FALSE POSITIVES, EXPERT ADVISORY STRUCTURE

DAY TWO:

UN-ANTICIPATED SIGNALS: What are the key long term CHANGES

- OTHER GOOD IDEAS: COMMUNITY PHARMACY NETWORK, LARGE SIMPLE SAFETY STUDIES, COMPUTER ASSISTED FEEDBACK LOOPS FOR ENHANCED REPORTING

DAY TWO:

UN-ANTICIPATED SIGNALS: What are the key short term initiatives?

- **FUND PILOTS LINKING LONGITUDINAL DATABASES**
- **GAIN EXECUTIVE MANDATES AND BROAD HHS SUPPORT**
- **BUSINESS CASE/ COST-EFFECTIVENESS FOR THESE RESOURCES; UTILITY RESEARCH**
- **FUND CENTERS OF EXCELLENCE (NODES)**

DAY TWO:

UN-ANTICIPATED SIGNALS: What are the key short term initiatives?

- COMMON DATABASE AND I.T. PLATFORMS
- WHAT ITEMS NEED TO BE INCLUDED IN DATABASES FOR SIGNAL DETECTION?
- PRODUCT LIABILITY AND SAFE HARBOR REFORM TO ENCOURAGE RESEARCH AND FULL EARLY DISCLOSURE

DAY TWO:

UN-ANTICIPATED SIGNALS: What are the key short term initiatives?

- **DEFINE KEY DATA STANDARDS AND ENSURE THAT THE KEY DATA ELEMENTS CAN BE LINKED**
- **ANOTHER THINK-TANK ESTABLISHING PRIORITIES ... THE PRIORITY DRUG SAFETY RESEARCH AGENDA**

DAY TWO:

UN-ANTICIPATED SIGNALS: What are the key short term initiatives?

- PROOF OF CONCEPT TO TEST DIFFERENT METHODS ON OBSERVATIONAL DATA
- GUIDELINES FOR A 'SIGNAL MANAGEMENT SYSTEM', INFORMATICS INFRASTRUCTURE
- SENSITIVE TECHNIQUE WITH ALGORITHM IN CLINICAL JUDGEMENT ... LOW COUNT SIGNALS ... HOW MUCH WORK DO THEY CREATE?

UN-ANTICIPATED SIGNALS: What are the key (UNIQUE) short term initiatives?

- ALL NME'S IN MULTIPLE SYSTEMS AND MANDATORY REGULAR REPORT TO ADVISORY COMMITTEES (DO AS A PILOT; EXPLORE COMPLEMENTARY METHODS)
- FDA CONTRACT WITH EXPERTS AND PARTNERS ... DO THE WORK EXTRAMURALLY
- DEVELOP ALGORITHMS FOR DESIGNATED MEDICAL EVENTS FOR APPROXIMATELY TWENTY CONDITIONS

DAY TWO:

UN-ANTICIPATED SIGNALS: What are the key short term initiatives?

- TEST VALIDITY OF (KNOWN) SIGNALS IN A VARIETY OF DATA BASES
- RADICAL TRANSPARENCY
- H.I.T. GRANTS AT AHRQ
- FRONT END PACKAGES FOR END USERS
- PROTOCOLS AND USE CASES FOR VALIDATION

DAY TWO:

UN-ANTICIPATED SIGNALS: What are the key short term initiatives?

- THINK TANK FOR DATA MINING TOOLS AND PROTOCOLS FOR VALIDATION
- PPP ... ADVISORY GROUP ON HOW TO MANAGE AND COMMUNICATE SIGNALS
- ... EVERY SIGNAL DETECTION STUDY BE ACCOMPANIED BY A SIMULTANEOUS CONFIRMATION STUDY
- GUIDELINES FOR EVALUATION

DAY TWO:

UN-ANTICIPATED SIGNALS: What are the key short term initiatives?

- WHAT IS THE APPROPRIATE/ACCEPTABLE FALSE POSITIVE FREQUENCY
- LEARN FROM THE GENETICS WORLD
- “... MEETINGS SUCH AS THIS ONE ARE A GOOD START”!

DAY TWO:

UN-ANTICIPATED SIGNALS: What are the most feasible NEXT STEPS?

- GET TO WORK, FOLKS!

DAY TWO:

SIGNAL EVALUATION: What are the key long term CHANGES

- MULTI-SECTOR ADVISORY COMMITTEE / GOVERNANCE BOARD
- METHODS DEVELOPMENT AND TESTING
- STANDARD PROCESSES
- DATA INTEGRATION AND DATA ACCESS
- INVEST MORE RESOURCES IN SIGNAL EVALUATION IN STRUCTURED DATA ... DE-EMPHASIZE SPONTANEOUS REPORTING

DAY TWO:

SIGNAL EVALUATION: What are the key long term CHANGES

- PLUS ...
- TRAINING CRITERIA, STANDARDS, CENTERS
- LOBBY CONGRESS FOR MORE MONEY FOR FDA AND EXTRAMURAL PROGRAMS
- DO AN IOM STUDY OF THE DRUG SAFETY SYSTEM
- BUILD INFORMED CONSTITUENCY DEMAND

SIGNAL EVALUATION: What are the key SHORT term CHANGES: MULTISECTOR ADVISORY COMMITTEE

- PROCESS FOR EVALUATING SIGNALS
- PRIORITIZING SIGNALS TO EVALUATE
- PROVIDING GUIDANCE ON SIGNAL INTERPRETATION
- PRIORITIZING RESOURCES
- USE NTSB APPROACH TO EVALUATE FAILURES
- PROVIDE GUIDANCE ON COMMUNICATION

SIGNAL EVALUATION: What are the key SHORT term CHANGES:METHODS

- LEARN FROM GENETICS
- CREATE INVENTORY OF METHODS THAT HAVE BEEN EVALUATED

SIGNAL EVALUATION: What are the key SHORT term CHANGES: STANDARD PROCESS

- GOLD STANDARD FROM RCTS REGARDING SAMPLE LIST OF DRUG-EVENT PAIRS, POSITIVE AND NEGATIVE SIGNALS LIST
- INDUSTRYWIDE PLACEBO DATABASE TO SERVE AS BACKGROUND FOR COMPARISON
- PROCESS FOR REPEATED LOOKS, HOW TO SELECT SIGNALS FOR FURTHER DETECTION
- QUICK ACCESS TO DATA AND CHARTS FOR VALIDATION

SIGNAL EVALUATION: What are the key short term initiatives? DATA INTEGRATION

- LINKAGE ACROSS EXISTING EMR, CLAIMS AND VITAL STATISTICS REGISTRY DATASETS
- LINKAGE OF PRE AND POST APPROVAL DATASETS
- ACCESS TO CHARTS FOR VALIDATION
- ACCESS TO DATA FOR STUDIES

SIGNAL EVALUATION: What are the key short term initiatives? TRAINING

- MORE WORKFORCE WITH MORE EPIDEMIOLOGIC AND QUALITATIVE SKILLS AND KNOWLEDGE OF DATA BASES
- COMPETENCY BASED TRAINING
- WORKFORCE NEEDS STUDY
- MORE CERTS AND 'BABY-CERTS'

DAY TWO:

SIGNAL EVALUATION: What are the most feasible NEXT STEPS?

- INVEST MORE IN REGISTRIES, LSTs, DE-EMPHASIZE SPONTANEOUS REPORTS AND REDUCE REPORTING REQUIREMENTS (OFFSET \$)
- MORE NEEDED ... it's up to YOU!

EVALUATION OF SIGNALS: MIND the GAP

- The BALANCE dilemma REMEMBER BENEFITS

The WAY FORWARD

- REFINE AND CLARIFY THE NEEDED ACTIONS ANALYSIS AND PROPOSALS FOR CLOSING/BRIDGING THE GAPS
- TOP of the TOP
- ACTION AGENDA! (Improve the talk to do ratio)
- ACTORS DESIGNATE: YOU/WHO
- FISCAL IMPLICATIONS and Game Plans

... and just when you thought it was safe: “other ...”

- Don't be shy about “new” thoughts ... or consolidated recommendations

Oh, great guru: What is the answer?



Oh, great guru: What is the answer?

- My son (er, um, daughter): what is the

question???