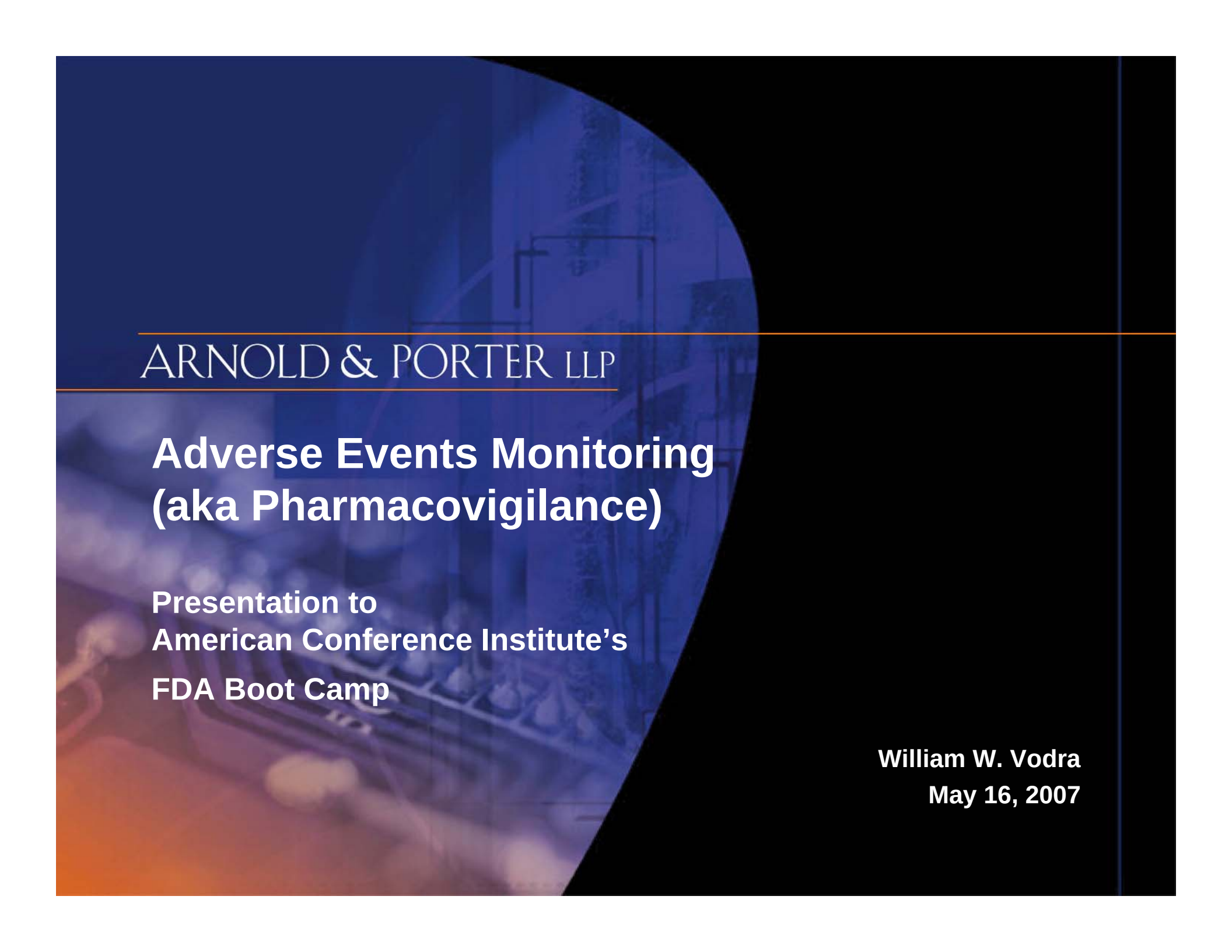




ARNOLD & PORTER LLP

Adverse Events Monitoring (aka Pharmacovigilance)

**Presentation to
American Conference Institute's
FDA Boot Camp**

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Agenda

- What is pharmacovigilance (PV)?
- How does PV use adverse event reports?
- What are the other tools for PV?
- How does PV relate to risk management overall?
- What are common areas of noncompliance?
- What are the risks from inadequate PV?

Key Terms

- Pharmacovigilance (PV)
 - Same as “post-marketing surveillance” (PMS) and “adverse event monitoring”
- Adverse drug reaction (ADR), adverse event (AE), adverse drug experience (ADE)
- Local = within country
- Global = on multinational basis

What is PV?

- Mixture of tools to detect and characterize risks and unexpected benefits
- Part of a larger drug safety universe, including risk management and benefit-risk decision-making

Why is PV Needed?

- Many effects not known at market entry
- Clinical trials before approval naturally limited
 - With 2-3000 patients, unlikely to see an event that occurs in less than 1 in 1,000 cases
 - Restricted patient populations (elderly, children, pregnant women, ethnic groups)
 - Short duration vs. latent risks
 - Interactions with other drugs, diseases, diet

Mixture of Tools

- Passive collections of spontaneous reports of adverse events
 - Active investigation and analysis
 - THE PRIMARY POST-APPROVAL TOOL
- Active observation of patient groups
 - Controlled clinical trials
 - Registries and cohort studies
- Epidemiological studies

The “New” Risk Management Universe

- Risks arise both from drug properties and from how drugs are selected, dispensed, and used by physicians and patients
 - Use in populations not adequately covered pre-approval
 - Use in larger numbers, for longer periods
 - Off-label uses
- Solution to unacceptable risk may not be removal of drug
 - Better control over use might reduce risk, increase benefits
 - Public health served by access to effective drugs, if risks can be managed to acceptable levels

The “New” Risk Management Universe

- Risk identification, characterization and quantification
- Risk confrontation (reassessment of benefit-risk ratio)
- Risk minimization techniques
 - Risk-benefit information (labeling for physicians, patients)
 - Intervention in prescribing and use of drugs
- Assessment of effectiveness of risk management

How Does PV Use ADE Reports? Six Phases

1. Detection and attribution
2. Report to company
3. Investigation by company
4. Analysis and use by company
5. Reporting by company to regulatory authorities
6. Evaluation and use by regulatory authorities

1. Detection

- Detection = Recognition of an adverse or unexpected health event after exposure to drug
 - Undesired event or failure of efficacy
- Factors affecting detection of ADE
 - Natural course of patient's disease, age
 - Ability to discern ADE has occurred
 - Uniqueness of ADE
 - Severity of event and outcome to patient
 - Structured ascertainment process

1. Attribution

- Attribution = Suspicion of an association between drug and event
- Factors affecting attribution
 - Background rate of event
 - Time between drug exposure and event
 - Newness of exposure for patient
 - Prior experience with drug and similar drugs
 - Whether event was expected (e.g., in labeling or seen with other similar drugs)

1. Detection and Attribution

- Who may detect and attribute?
 - Patient or family member
 - Health care professional (physician, nurse, pharmacist)
 - Plaintiffs' lawyers
- Is anyone legally responsible to do so?
 - Generally not -- but health care professionals may be obligated to report in some instance

2. Reporting to Company

- A. Solicited direct reports
- B. Spontaneous direct reports
- C. Indirect reports

2.A Company-solicited Direct Reports

- Solicited reports also come in many forms
 - Clinical studies
 - “Market seeding” studies
 - Market research surveys
 - Sales representative activities
- Companies may not be aware of the existence of “solicited” reports in their files

2.A Company-solicited Direct Reports

- Most solicited reports are also voluntary
 - Physician or other professional under no contractual duty to report, except in clinical trials
- Legal duty may exist in special situations
 - Local laws or restrictions on use of specific drugs, clinical trials

2.B Spontaneous Direct Reports

- Spontaneous reports can occur in many forms, not just as a “report”
 - Complaints from consumers
 - Inquiries by health care professionals
 - Interactions between sales representatives and medical professionals
 - Lawsuits

2.B Spontaneous Direct Reports

- FDA defines a “report” as containing 4 elements
 - Identifiable reporter (someone who claims to have first-hand information)
 - Identifiable patient (someone who actually used the drug and had the event)
 - Identifiable medical event (harm or failure of efficacy)
 - Identifiable drug or drugs

2.B Spontaneous Direct Reports

- Most spontaneous reporting is voluntary
 - Health care professionals may have professional obligation, but a legal requirement is infrequent
 - Local culture and practices very influential; Spontaneous reporting may be affected by medical training, easy reporting mechanisms
- In some countries, reporting may be either to government or to company, or both

2.C Indirect Reports

- Multiple potential sources
 - Medical literature
 - Public media (radio, TV, newspapers, Internet)
 - Other companies (e.g., licensees, co-marketers, or events with concomitant drugs)
 - Government agencies (e.g., direct reporting to government, with output to companies)

2.C Indirect Reports

- Companies responsible for what they know and what they reasonably could know
 - Routine monitoring of medical literature
 - Variable monitoring of local media
 - Not necessarily monitoring Internet
- May need routine information flow from government to company regarding ADR reports made directly to the government

3. Investigation by Company

- Initial reports often lack critical information
- Companies are responsible for making reasonable efforts to obtain missing information
 - Generally, patients and health care professionals do not have a legal duty to provide more information
 - Key is to persuade reporter of value of information to public health

3. Investigation by Company

- Investigations are usually done locally
 - Language and cultural sensitivities
 - Understanding of local medical practice and terminology
- FDA has proposed that investigations involving physician reports be investigated by a company physician

3. Investigation by Company

- In global companies, information is usually transmitted to a central drug safety unit at corporate HQ
- Information must be “translated” into standard terms for processing after investigation
- Local reporting to corporate HQ governed by national rules on privacy of patient records

3. Investigation by Company

- Most global companies have a central drug safety unit in corporate HQ
 - Establish standard procedures, terminology
 - Train personnel
 - Receive and evaluate local reports
 - Assure quality and consistency of operations
- These global units usually have highly trained and skilled professionals

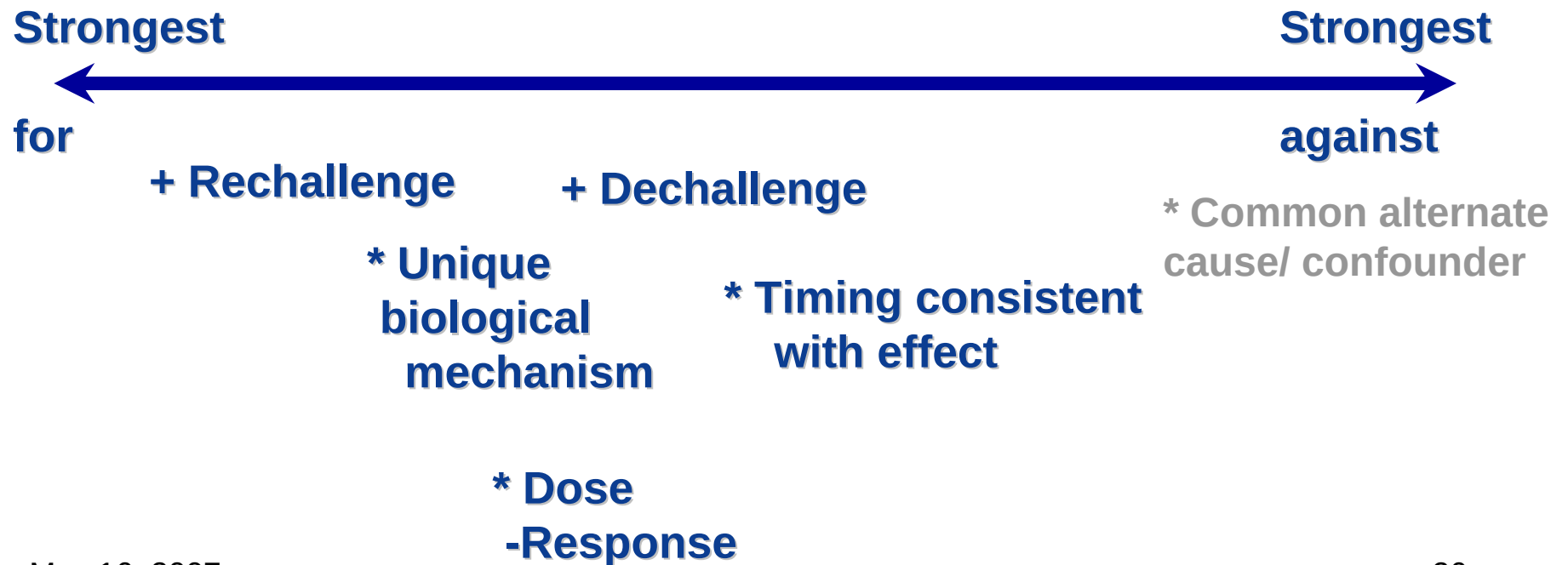
4. Analysis by Company

- Analysis of individual cases
 - Seriousness of event
 - Objective tests
 - Subjective “important medical event” test
 - Unexpectedness of event
 - Comparison to labeling (package insert)
 - Comparison to similar drugs
 - Degree of association
 - Can causality be excluded?
 - Assessing strength of association

4. Analysis by Company

Components of ADE causality assessment

(Thanks to Dr. Judy Jones, the Degge Group, for this slide.)



4. Analysis by Company

- Evaluation of multiple cases
 - Looking for patterns
 - Looking for consistency of strength of association
- Spontaneous reports cannot be converted into incidence rates
 - Too many variables in detection, attribution, reporting
 - Absence of appropriate denominator data
- ADE processing is a Good Manufacturing Practice (GMP) requirement

5. Reporting by Company

- Reporting to national authorities governed by local law
 - Collect globally, report locally
- Global database used to identify and prepare local reports
 - Frequent misunderstanding: “Local rules govern reports both to local authorities and to corporate HQ” -- NOT TRUE

5. Pre-approval Reporting by Company to FDA

- Expedited reporting of each “serious and unexpected” ADE received from any source for which there is a “reasonable possibility” that the drug may have caused the ADE
 - 15 days from when the company receives the information (not makes the causality determination)
- Annual reports summarizing the most frequent and most serious ADEs, all deaths, and all drop-outs for ADE reasons

5. Post-approval Reporting by Company to FDA

- No causality assessments for spontaneous reports
- Expedited reporting of each “serious and unexpected” ADE received from any source
 - 15 days from when company learns of the ADE
 - Special system for vaccines (CDC involved with FDA)
- Periodic reporting of all other spontaneous domestic ADEs
 - Foreign “non-serious” or “serious but expected” cases need not be reported
 - Periodic reports due quarterly for first 3 years post-approval, annually thereafter

What is an “Unexpected” ADE?

- Objective test: an event that is not listed in the current US product labeling or investigational brochure
- An event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs because of greater severity or specificity
- Example:
 - Hepatic necrosis versus elevated hepatic enzymes

What is a “Serious” ADE?

- An event associated with a drug that
 - Resulted in an objective clinical outcome
 - Death
 - Persistent of significant disability or incapacity
 - Congenital anomaly or birth defect
 - In-patient hospitalization or prolongation of existing hospitalization, or
 - Was life-threatening to the person who had the event
 - Or, is an “important medical event”

What is a “Life-Threatening” ADE?

- Creates an immediate risk of death when the event occurred
- It does not include an ADE that, had it occurred in a more severe form, might have caused death but as it actually occurred did not create an immediate risk of death (objective, not speculative, test)
- Example:
 - An allergic reaction resulting in rash would not be life-threatening, even though anaphylaxis can be fatal

What is an “Important Medical Event”?

- Subjective test: An event which is not “serious” by other criteria but which based upon appropriate medical judgment might jeopardize the patient and may require medical or surgical intervention to prevent one of the serious outcomes
- Examples:
 - Allergic bronchospasm requiring intensive treatment
 - Blood dyscrasias or convulsions not resulting in hospitalization

Special Rules on ADE Reporting

- Post-approval studies
 - Report only if “there is a reasonable possibility that the drug caused the adverse experience”
- Scientific literature reports
 - Report only serious and unexpected ADEs in scientific or medical journals

6. Evaluation by Regulatory Authorities

- Regulatory and health authorities review reports
 - Compare, contrast and integrate with reports on similar products
 - Look for patterns, relative differences among products
- Authorities may initiate their own research programs to study issue further

6. Use by Regulatory Authorities

- Authorities may use the information to make regulatory decisions
 - Request company use other PV tools
 - Require labeling changes
 - New Warnings
 - Restrictions on indications
 - Require risk minimization plans
 - Remove the product from the market

Limits of Spontaneous Reports

- Spontaneous ADE reports rarely can demonstrate
 - causation
 - incidence
 - risk relative to background rates
 - patient-specific risk factors
- They can generate a hypothesis (a “signal”), and PV can use other tool to test that hypothesis

Description

- Active observation of patient groups
 - Registries of patients
 - Prospective cohort studies
- Epidemiological studies
 - Case-control
 - Retrospective cohort studies
- Preclinical and clinical trials
 - “Large simple safety study”
 - Meta-analyses of multiple studies

Four Elements of Risk Management

1. Identification, characterization and quantification of risk
 - Purpose of PV
2. Risk confrontation (reassessment of benefit-risk ratio)
3. Risk minimization techniques to intervene in prescription and use of drugs
4. Benefit-risk information (for physicians, patients)

Risk Confrontation

- In light of new risk profile, is the benefit-risk ratio still favorable?
- Brings benefit squarely into the equation
 - No risk-free drugs
 - Addresses the concern that regulators only worry about risk
- Continuous evaluation throughout life of drug

Risk Minimization

- Recognizes that drugs are used in the “real world”
- Wide variations in many other critical factors
 - Physician skills
 - Supporting HCP and medical facilities
 - Patient education and cultural attitudes
 - Chances for simple errors
- Goal is to find ways to supplement skills and communications and prevent errors

Risk Minimization Tools

- Tools can be tailored to the specific risk and situation
- Tools include:
 - Patient education and consent
 - Mandatory lab tests before and during drug use
 - Restriction of access to drug to certain specialists or clinical settings
 - Packaging and labeling to prevent confusion

Risk Communication

- Communication to prescribing physician
- Communication to other healthcare professionals (pharmacists, nurses, lab technicians)
- Communications to patients
- Issues:
 - Effectiveness of individual communications
 - Information overload

Closing the Loop

- Final aspect: Assessment of efficacy of risk management
- Are risks being reduced or confined to levels deemed acceptable during the risk confrontation stage?
- Are the controls on drug utilization effective, adequate, unnecessary?
- Are the communications effective in affecting behavior?

Conclusions

- PV is a complex and highly technical area
- Its importance is growing, as FDA and other agencies seek to maximize benefits and reduce risks
- Poor execution can expose a company to regulatory sanctions, but more importantly to product liability risks
 - In any drug disaster, FDA and the public ask, “What did the company know and when did they know it?”
 - Good PV procedures may provide a persuasive answer to that question

Questions

- The floor is open for discussion
- Thank you for your participation
- If you have questions later, you may reach me at:

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Important Sources of Information

- 21 C.F.R. 312.32 (IND)
- 21 C.F.R. 314.50(d)(5)(vi)(b) (safety updates)
- 21 C.F.R. 314.80 (NDA)
- 21 C.F.R. 310.300 (non-NDA)
- 21 C.F.R. 211.198 (GMP)
- ICH, Federal Register notices, FDA guidances