

Interpretation of Clinical Safety Data
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Public Domain

OBJECTIVES

- **To explain differences in approaches to safety data and efficacy data**
- **To demonstrate that adequate attention needs to be given to the assessment, analysis, and reporting of adverse events to permit valid assessment of potential risks of intervention**

OBJECTIVES

- **To highlight the distinctions between rare, serious adverse events and common, non-serious adverse events**
- **To define terms commonly used in the description of adverse events**
- **To explain methods by which causality for adverse events can be assessed**

OBJECTIVES

- **To illustrate these concepts with examples from NDAs and BLAs**

Principal References

- **Temple RJ, Jones JK, and Crout JR.**
Adverse effects of newly marketed drugs.
N Engl J Med 1979;300(18):1046-7.
- **Spilker, Bert. (1991): *Guide to Clinical Trials*.** Raven Press, New York;
Chapters 71-83.

Adverse Effects of Newly Marketed Drugs

- **New drugs are marketed on the basis of comparatively limited safety information**
- **Effectiveness: expected result, prespecified endpoint(s)**
- **Safety: open-ended, uncertain endpoint(s)**

Adverse Effects of Newly Marketed Drugs

- **Some risks can be anticipated (e.g., aminoglycosides and ototoxicity)**
- **Even infrequent adverse events (1 per 1000) are of interest if serious**
- **Other risks are screened for routinely (e.g., hepatic, renal, hematologic)**
- **But some risks may be missed**

Adverse Effects of Newly Marketed Drugs

- **Events that may be missed**
 - **rare events**
 - **events occurring after long-term use**
 - **events occurring in special groups**
 - **events occurring in association with specific diseases**
 - **events occurring in association with concomitant therapy**

Adverse Effects of Newly Marketed Drugs

- **Common adverse events are generally identified in prospective trials**
- **Infrequent or delayed adverse events require special techniques (e.g., case-control studies, cohort studies)**

Adverse Effects of Newly Marketed Drugs

- **Isolated reports can be definitive in associating a drug with an adverse effect**
 - **if drug administration and the event are temporally related;**
 - **if the event disappears when the drug is stopped (dechallenge), and;**
 - **if the event reappears when the drug is readministered (rechallenge).**

Ascertainment of Adverse Events

- **Spontaneously reported symptoms**
- **Symptoms reported as a result of a probe**
- **Both**

Spontaneously Reported Symptoms

- **Example: “Have you had any health problems since your last visit?”**
- **Advantages**
 - Tends to detect the more “severe” episodes
 - May detect truly unexpected adverse events
 - Identifies what’s important to the patient
- **Disadvantages**
 - Lacks standardization (e.g., within and across trials)

Symptoms Reported Because of a Probe

- **Example: “Checklist” of Adverse Events**
- **Advantages**
 - **Allows standardization within and across trials)**
- **Disadvantages**
 - **May miss unexpected adverse events**

Domains used to Describe Adverse Drug Events

- **Objectivity (e.g., symptoms vs. laboratory tests)**
- **Seriousness (e.g., non-serious vs serious)**
- **Predictability (e.g., expected vs. unexpected)**
- **Attribution to therapy (e.g., ADE vs. ADR)**
- **Intensity (e.g., mild vs. severe)**
- **Incidence (e.g., rare vs. common)**
- **Latency (e.g., short-term vs. delayed)**

Objectivity and Subjectivity

- **Objective**
 - **Perceptive to the external senses**
- **Subjective**
 - **Pertaining to or perceived only by the affected individual; not perceptible to the senses of another person**
 - **Dorland's Illustrated Medical Dictionary, 28th Edition**

Adverse Drug Events: Objectivity

- **Adverse reactions that are measured primarily in numerical or objective terms**
 - **Clinical laboratory abnormalities detected in biological samples**
 - **Clinical laboratory abnormalities detected in the patient**
 - **Abnormalities detected on physical exam**

Adverse Drug Events: Objectivity

- **Caution: Just because a scale is numerical doesn't necessarily mean it's an objective scale. It may be pseudo-quantitative.**
- **Example: Visual analog scale (VAS) for assessment of pain (a subjective endpoint).**

Adverse Drug Events: Subjectivity

- **Caution: Just because a symptom is subjective doesn't mean that it's not real or important**
- **Adverse reactions may also be described in subjective and/or descriptive terms**
- **Examples: pain, nausea**

FDA Definitions

Location in CFR

- **21 CFR 312.32 (IND regulations)**
- **21 CFR 310.305 (Marketed Rx Drugs, no NDA)**
- **21 CFR 314.80 (NDA regulations)**
- **21 CFR 201.57(g) (Labeling regulations)**

FDA Definitions

Adverse Drug Experience

- **Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose, whether accidental or intentional; ...**

FDA Definitions

Adverse Drug Experience (continued)

... an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacologic action.

-21 CFR 314.80

-21 CFR 310.305

FDA Definitions

Associated with the use of the drug

- **There is a reasonable possibility that the experience may have been caused by the drug**

-21 CFR 312.32

FDA Definitions

Disability

- **A substantial disruption of a person's ability to conduct normal life functions**

-21 CFR 312.32

-21 CFR 314.80

FDA Definitions

Life-threatening Adverse Drug Experience

- **Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.**

-21 CFR 312.32

FDA Definitions

Serious Adverse Drug Experience

- **Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability / incapacity, or a congenital anomaly / birth defect...**

FDA Definitions

Serious Adverse Drug Experience (cont.)

... Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition....

FDA Definitions

Serious Adverse Drug Experience (cont.)

...Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

-21 CFR 312.32

-21 CFR 314.80

FDA Definitions

IND: Unexpected Adverse Drug Experience

- **Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended...**

FDA Definitions

Unexpected Adverse Drug Experience (cont.)

...For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis...

FDA Definitions

Unexpected Adverse Drug Experience (cont.)

...Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue or greater specificity) if the investigator brochure only listed cerebral vascular accidents...

FDA Definitions

Unexpected Adverse Drug Experience (cont.)

...”Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

FDA Definitions

NDA: Unexpected Adverse Drug Experience

- **Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity...(as in IND regulations)**

-21 CFR 314.80

FDA Definitions

Adverse Reactions

- An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.**

-21 CFR 201.57(g)

Serious Adverse Events Identification

- **Deaths**
- **Those reported as serious**
- **Withdrawals from clinical trials deserve scrutiny (e.g., dropouts because of adverse events)**

Adverse Events IND Safety Reports

- **Unexpected fatal or life-threatening**
 - **by phone or facsimile within 7 calendar days**
- **Serious and unexpected (human), or**
- **Animal findings that suggests significant risk for humans (e.g., mutagenicity, teratogenicity, carcinogenicity)**
 - **written, both within 15 calendar days**
- **Follow-up reports--as soon as available**

Adverse Events

IND Annual Reporting

- **Most frequent and most serious AEs by body system**
- **List of subjects who died, including cause**
- **List of subjects who dropped out in association with an adverse experience**

Adverse Events Postmarketing Reports

- **15-day alert reports**
 - **Serious and unexpected AEs**
 - written, within 15 calendar days
 - foreign or domestic
- **Followup to 15-day alert reports**
 - **Written, within 15 calendar days**

Adverse Events Postmarketing Reports

- **Periodic adverse drug experience reports**
 - **Quarterly for 3 years from date of approval**
 - **Then annually**

Adverse Drug Events Attribution to Therapy

- **A Commonly Used Scale**
 - **Definitely related**
 - **Probably related**
 - **Possibly related**
 - **Not related**
 - **Unknown**

Adverse Drug Events Severity

- **Severity is a measure of intensity (e.g., mild, moderate, severe pain)**
- **Severity is not synonymous with seriousness**

Adverse Drug Events: Incidence

- **The likelihood of observing an adverse reaction depends on several factors**
 - **incidence of the medicine-induced reactions**
 - **the background incidence of the adverse reaction in the population**
 - **the number of patients evaluated**

Adverse Drug Events: Incidence

- **ICH Guideline**

- **It is expected that short-term event rates (cumulative incidence of about 1%) will be well characterized**
- **The safety evaluation during clinical drug development is not expected to characterize rare adverse events, for example, those occurring in less than 1 in 1,000 patients**

Adverse Drug Events: Incidence/Latency

- **ICH guideline (continued)**
 - **Most ADEs occur within the first 3 to 6 months of drug treatment. The number of patients treated for 6 months at dosage levels intended for clinical use should be adequate to characterize the pattern of ADEs over time...**

Adverse Drug Events: Incidence/Latency

- **ICH guideline (continued)**
 - **To achieve this objective the cohort of exposed subjects should be large enough to observe whether the more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). Usually from 300-600 patients should be adequate.**

Adverse Drug Events: Incidence/Latency

- **ICH guideline (continued)**
 - **Some serious ADEs may occur only after drug treatment for more than 6 months. Therefore, some patients should be treated with the drug for 12 months. One hundred (100) patients treated for one year is considered to be acceptable.**

Adverse Drug Events: Incidence/Latency

- **ICH guideline (continued)**
 - **It is anticipated that the total number of individuals treated with the investigational drug, including short-term exposure, will be about 1500.**

Systems for Classifying Diseases and Adverse Events

- **Allows investigator(s) to classify the same adverse event with the same term**
 - Same investigator, same patient
 - Same investigator, different patients
 - Different investigators, same patient
 - Different investigators, different patients
- **Allows investigator(s) to classify different adverse events with different terms**

Systems for Classifying Diseases and Adverse Events

- **Medical Dictionary for Drug Regulatory Affairs (MEDDRA)**
- **Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART)**
- **World Health Organization (WHO) Adverse Reaction Terminology**
- **International Classification of Diseases (ICD-9)**
- **Medical Subject Headings (Medline)**

Systems for Classifying Diseases and Adverse Events

- **Modified Thrombolysis in Myocardial Infarction (TIMI) criteria**
 - **Rao AK et al. J Am Coll Cardiol 1988; 11(1):1-11.**
 - **The EPIC Investigators. N Engl J Med 1994;330:956-61.**

Systems for Classifying Diseases and Adverse Events

- **Major bleeding**
 - **Intracranial bleeding, or**
 - **Bleeding associated with a decrease from baseline of hemoglobin by at least 5 g/dl (or when hemoglobin was not available, a hematocrit decrease of at least 15%)**

Systems for Classifying Diseases and Adverse Events

- **Minor bleeding**
 - Spontaneous and observed blood loss as gross hematuria or hematemesis, or
 - Observed blood loss whether spontaneous or nonspontaneous, with a decrease from baseline of hemoglobin by at least 3 g/dl (or when hemoglobin was not available, a hematocrit decrease of at least 10%), or...

Systems for Classifying Diseases and Adverse Events

- **Minor bleeding (continued)**
 - A decrease from baseline of hemoglobin by at least 4 g/dl (or when Hgb was not available, a Hct decrease of at least 12%) with no bleeding site identified despite an effort to find one
- **Insignificant bleeding**
 - Blood loss insufficient to meet the criteria for minor bleeding

Systems for Classifying Diseases and Adverse Events

- **Systematized Nomenclature of Medicine (SNOWMED)**
- **DSM-IV (psychiatry)**
- **Diagnosis-related Groups (DRGs)**
- **Pharmaceutical company provides a customized, standardized dictionary of terms**

Adverse Events: Establishing Causality

- **Statistical analyses**
 - **Often particularly useful for evaluation of common adverse events**
 - **Generally require comparison groups**

Adverse Events: Establishing Causality

- **Statistical analyses (continued)**
 - **Assessments of central tendency (e.g., means, medians, modes) are often uninformative for infrequent adverse events; the outliers are usually of greatest interest (the “action” is with a few)**
 - **May provide point estimate and confidence intervals for adverse events, regardless of whether or not they are common**

Adverse Events: Establishing Causality

- **Statistical analyses (example)**
 - **The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994;330:956-61.**

EPIC Experimental Design

- **Randomized, double-blind, placebo-controlled, 56 centers**
- **2099 patients at high risk of abrupt vessel closure during or after PTCA**
- **Parallel design with three arms**
 - **Placebo bolus and placebo infusion**
 - **c7E3 Fab bolus and placebo infusion**
 - **c7E3 Fab bolus and c7E3 Fab infusion**

Adverse Events: Establishing Causality

- **Global introspection (Bert Spilker)**
 - **Experts consider all of the relevant data in a specific case, including data obtained at their request (e.g., concomitant laboratory data, effects of dechallenge and rechallenge), and reach an opinion on the cause-effect relationship. The overall judgment is based on knowledge of the case and the experience and intuition of the experts.**

Adverse Events: Establishing Causality

- **Step 1: Categorize evidence by the quality of its sources**
- **Step 2: Evaluate the evidence of a causal relationship using standard guidelines**

Adverse Events: Establishing Causality

- **Quality of sources**
 - **Clinical trials**
 - **Cohort or case-control studies**
 - **Time-series studies**
 - **Case-series**

Adverse Events: Establishing Causality

- **Quality of Sources (continued)**
 - **The word “quality” incorporates consideration of study design, control groups, randomization, blinding, appropriate patient population, outcome measures, study size, etc..**

Adverse Events: Establishing Causality

- **Standard guidelines**
 - **Temporal relationship**
 - **Strength of association (e.g., RR, OR)**
 - **Dose-response relationship**
 - **Replication of findings**
 - **Biologic plausibility**

Adverse Events: Establishing Causality

- **Standard guidelines (continued)**
 - **Consideration of alternate explanations**
 - **Cessation of exposure**
 - **Specificity of the association**
 - **Consistency with other knowledge**

Adverse Events: Establishing Causality

- **Global introspection**
 - **Example: Trandate/Normodyne (labetalol) and Unicard (dilevalol)**
 - **Labetalol is composed of 4 stereoisomers. One of these, dilevalol (the R,R' isomer) was withdrawn from worldwide distribution on 9 August 1990 after several patients developed hepatic complications.**

Adverse Events: Establishing Causality

- **Labetalol**
 - **Labetalol was shown to have hepatotoxicity in an analysis of postmarketing reports (Clark JA et al. Annals of Internal Medicine. 1990;113:210-3.)**
 - **At the time of publication, 11 cases, 3 of which were fatal had been reported in the United States**

Adverse Events: Establishing Causality

- **Labetalol**

- **Dechallenge: 9 patients improved after cessation of labetalol therapy**
- **Rechallenge: 1 patient had a recurrence after therapy was restarted**
- **No historic or laboratory evidence for other viral, toxic, or drug-induced causes of hepatocellular damage**

Adverse Events: Establishing Causality

- **Labetalol**
 - **Demographic/historic data were not consistent with an etiology of non-A, non-B hepatitis**
 - **In the 5 cases where histologic evaluation was performed, 4 were consistent with hepatocellular necrosis and 1 with chronic hepatitis**

Adverse Events: Establishing Causality

- **Labetalol**
 - **The mean latency for the initial event was 60 days (range: 21-189 days)**
 - **Six additional cases were reported to the FDA from abroad, but were not included in the analysis because of the difficulty of obtaining follow-up data**

Adverse Events: Establishing Causality

- **Labetalol**
 - **The authors concluded that the clinical presentation was most compatible with a metabolic idiosyncrasy, but could not entirely exclude other pathogenic explanations.**

Adverse Events: Establishing Causality

- **Labeling warning for Trandate HCl (labetalol)**
 - **Hepatic Injury: Severe hepatocellular injury, confirmed by rechallenge in at least one case, occurs rarely with labetalol therapy. The hepatic injury is usually reversible, but hepatic necrosis and death have been reported...**

Adverse Events: Establishing Causality

- **Labeling warning (continued)**
 - **Injury has occurred after both short- and long-term treatment and may be slowly progressive despite minimal symptomatology. Similar hepatic events have been reported with a related research compound, dilevalol HCl, including two deaths. Dilevalol HCl is one of the four isomers of labetalol HCl...**

Adverse Events: Establishing Causality

- **Labeling warning (continued)**
 - Thus, for patients taking labetalol, periodic determination of suitable hepatic laboratory tests would be appropriate. Appropriate laboratory testing would be done at the first symptom/sign of liver dysfunction (e.g., pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness, or unexplained “flu-like” symptoms)...

Adverse Events: Establishing Causality

- **Labeling warning (continued)**
 - **If the patient has laboratory evidence of liver injury or jaundice, labetalol should be stopped and not restarted.**