

Assessing Drug Safety Data: Key Concepts & Issues

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Public Domain



OBJECTIVES

- **How safety is assessed during clinical trials**
- **How safety is assessed post-marketing**
 - **regulatory definitions & requirements**
 - **causality assessment**
 - **conduct of surveillance**
 - **roles of healthcare providers, industry & FDA**

Safety Assessment during Clinical Trials (I)

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

Clinical Trials (II)

- **Anticipated risks (e.g., aminoglycosides and ototoxicity)**
- **Risks of concern (e.g., hepatic, renal, hematologic, cardiac/QTc)**
- **Serious adverse events of particular concern even if infrequent (1 per 1000)**
– *some risks may be missed*

Clinical Trials (III)

- **Events that may be missed**
 - rare events
 - events occurring after long-term use
 - events occurring in special populations
 - events occurring in association with specific diseases
 - events occurring in association with concomitant therapy
- **ICH Pharmacovigilance Planning Guideline - 2003**

Clinical Trials (IV)

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

Clinical Trials (V)

- **Case 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).**

Clinical Trials (VI)

- **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**

Clinical Trials (VII)

- **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**

Clinical Trials (VIII)

- **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.**

Clinical Trials (IX)

- **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.**

Clinical Trials (X)

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

Clinical Trials (XI)

- It is anticipated that the total number of individuals treated with the investigational drug, including short-term exposure, will be about 1500.
- ICH Guideline: *“The Extent of Populations Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions (E1)”*

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)**

FDA Definitions

Code of Federal Regulations (CFR)

- **21 CFR - “Food and Drugs”**
 - **21 CFR 312.32 (IND Safety Reports)**
 - **21 CFR 310.305 (AE Reports for Marketed Rx Drugs, no NDA)**
 - **21 CFR 314.80 (Postmarketing Reports of AEs)**
 - **21 CFR 201.57 (Prescription Drug Labeling)**

FDA Definitions

- **Adverse Drug Experience (ADE)**
 - associated with use of drug
- **Serious ADE**
- **Unexpected ADE**

IND Safety Reporting Requirements

- **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**

IND Annual Safety Reporting

- **Required of all IND holders**
- **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**

Postmarketing Reporting Requirements

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

Postmarketing Reporting Requirements (II)

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

Establishing Causality

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

Establishing Causality (II)

- **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**

Establishing Causality (III)

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

Establishing Causality (IV)

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

Establishing Causality (V)

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

Establishing Causality (VI)

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

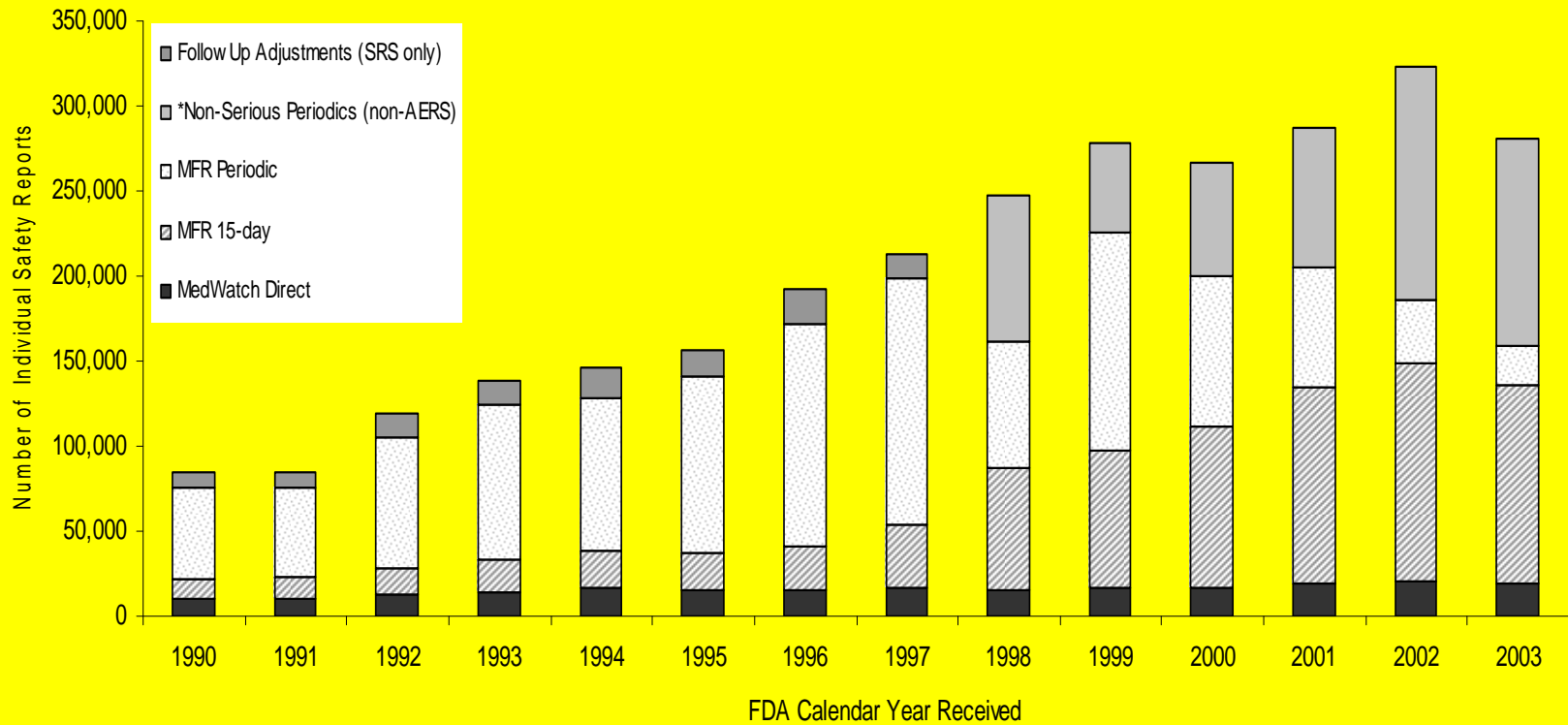
Establishing Causality (VII)

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

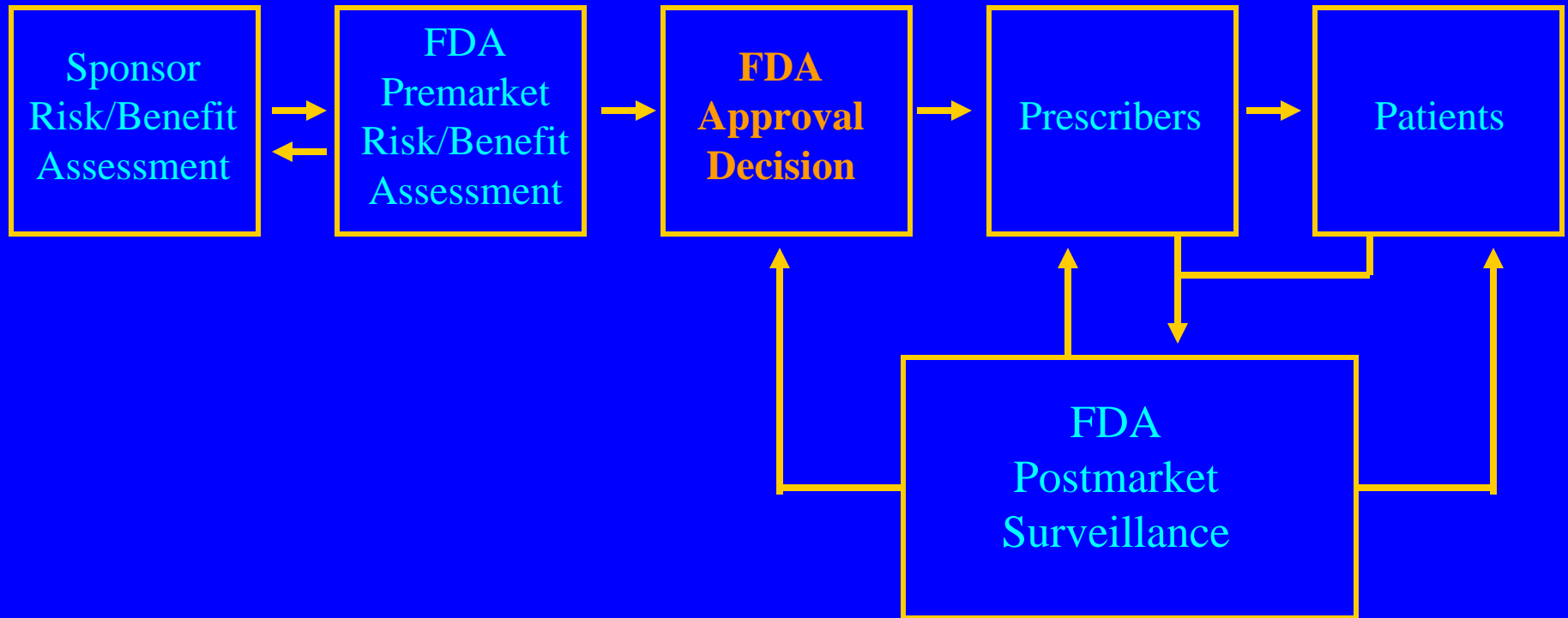
Adverse Event Reports

CDER Post-Marketing Adverse Event Reports Received

AERS Database/PSI Reporting for November 18, 2003.



System for Managing Risks - FDA Approval



Improving Postmarketing Risk Assessment

- Applying new tools/gathering better data
 - observational trials
 - targeted post-approval studies
- Active/sentinel event surveillance
- Drug utilization databases
- Medication error prevention

Questions

- MedWatch website
 - <http://www.fda.gov/medwatch/index.html>
 - partners/e-list
- Contact information
 - seligmanp@cder.fda.gov
 - 301-827-6276