
Regulatory Statistical Perspectives on Safety Issues in Drug Development

C. George Rochester, Ph.D.
Lead Statistician for Drug Safety Evaluation
Food & Drug Administration, Rockville, MD, USA
RochesterG@cder.fda.gov
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Disclaimer

The views expressed in this presentation are expressly those of the speaker and must **NOT** be taken to provide official policy or guidance on behalf of the FDA

Overview of Presentation

- I. General considerations
- II. Issues related to data generation
- III. Formulating a safety analysis plan
- IV. Information synthesis
- V. Temporal considerations in safety analysis
- VI. Summary

I. General Considerations

The FDA is responsible for the evaluation of efficacy, as well as, safety, which inherently embodies many uncertainties.

We must confront the challenge of approving therapeutics which offer a benefit for many and may simultaneously produce detrimental effects for a few.

Appropriate data upon which to make a determination of both efficacy and safety are critical to review and decision making.

Judgments about risks are always evaluated in conjunction with the benefit(s) of the product

It is estimated that adverse drug reactions (ADRs) caused 100,000 deaths among hospitalized patients in the USA in 1994 (* 4th leading cause of death)

(**Lazarou et al. JAMA 1998; 279:1200-1205**)

Definitions Risk Analysis Terms

Demonstration of safety is required by the Food, Drug and Cosmetic Act

Risk: the potential for a drug to adversely affect the health of individuals or populations following exposure.

Risk assessment: quantitative approaches to estimate health risks to individuals or populations from exposure to drug products. Goal is to provide information to improve the identification, estimation, and evaluation of the nature and severity of risks associated with a product.

Risk management: maps information obtained via risk assessment to choices of actions to minimize risk. Risk management includes risk acceptance, risk avoidance, or risk mitigation.

Risk communication: characterizes and presents information about risks and uncertainties to decision-makers and stakeholders.

Stakeholders

Regulators

- Risk assessment
- Risk minimization
- Risk communication

Sponsors

- Responsible for products
- Risk characterization
- Risk management

THE PUBLIC

Health Professionals

- Prescribers
- Clinical investigators

Others

- Pharmacovigilance experts
- Politicians
- Oversight bodies: IRB, DSMB
- Participants in clinical trials

Objectives of Safety Data Analysis

Identify and characterize safety aspects as early as possible

Identify risk factors related to increased toxicity and lack of efficacy

Describe temporal relations of adverse drug experiences and exposure

To provide data to support appropriate labeling of drugs and prevent costly consequences if marketed

II. Generating Appropriate Safety Data in Clinical Trials

In a typical trial designed primarily to show efficacy, approximately 85% of the data collected, is safety data. We probably collect too much data but not necessarily the most appropriate data upon which to base safety decisions.

The appropriate database to demonstrate the safety of a product is product-specific and depends on:

- **Proposed indication:** life-threatening or lifestyle enhancement
- **Intended duration of use:** short-term or long-term, intermittent or recurrent use
- **Diverse population:** age, race, gender, geography, concomitant drugs and concomitant diseases should be considered. The population which is likely to take drug should be reflected in the database - inclusion/exclusion criteria should be less restrictive

Domains of Safety Data Collected

Usual Safety Data Domains in the Pre-marketing Database

Exposure

Dropouts and reasons for discontinuation drug/study

Adverse events (SAE, TEAE) - with or without attribution to study drug, severity most often uninterpretable

Clinical laboratory measurements

Vital signs, ECGs, Concomitant disease and drugs

Special Safety Data

Special population safety studies (hepatic impairment)

Large simple safety studies

Critical Toxicities Relevant to Every New Drug

All new drugs must evaluate the potential for the following effects:

- QT prolongation
- Hepatotoxicity
- Nephrotoxicity
- Bone marrow toxicity
- Drug-drug interactions
- Polymorphic metabolism

Consult with the reviewing division during drug development - Pre-NDA meeting is too late!

When might Additional Safety Data become Necessary?

FDA has not issued guidance on safety for short-term use products: We encourage open and early communication - advisable to obtain agreements on a feasible course of action.

Additional data may be necessary:

- **Case-by-case** basis in consultation with review division. A very safe alternative exists and the benefit of the new drug is marginal
- Pediatric products and counter-terrorism agents
- Safety signals emerged during clinical development
 - **Consider a large simple safety study pre-marketing**
- Potential for rapid uptake into the marketplace and wide off label use

III. Formulating a Safety Data Analysis Plan

In order to achieve the objectives of the safety analysis as described previously a safety analysis plan is necessary. The plan relies on formal processes for data generation and analysis.

One should start thinking of safety during the earliest phases of drug development.

It deserves the same level of rigor that is often bestowed upon the demonstration of efficacy.

Although largely exploratory there is some structure to good safety data generation and analysis.

When might one consider a safety analysis plan?

When to Formulate a Safety Plan

Pre-clinical	Phases 1 & 2	Phase 3	LSSS*
<ul style="list-style-type: none"> •New compound •Similar molecules •Proteomics •Genomics •Animal data •Identify potential target toxicities 	<ul style="list-style-type: none"> •Special safety studies •Dose response exploration •PK/PD 	<ul style="list-style-type: none"> •Large efficacy studies •Careful ascertainment of safety outcomes •Integrated summary of safety 	<ul style="list-style-type: none"> • Risk management plan • Population impact analysis • Risk management plan formulated
<p>++SAFETY PLAN</p>		<ul style="list-style-type: none"> •AESI •LSSS* <p>(e.g., 25,000 US patient study)</p>	

*LSSS= Large Simple Safety Study

What should the Safety Plan Contain?

There is a clear distinction to be made between clinical practice and clinical trials. Trials are guided by a protocols which stipulate:

- The data should be obtained
- Specify anticipated AESI or SAE (varies based on population being studied, e.g., pediatrics or elderly)
- Describe the minimum data to be collected if certain pre-defined thresholds are exceeded, input from clinical experts useful (e.g., hepatitis)
- Formalized algorithms to foster consistency across centers and investigators
- Process for **complete** (planned and unplanned) and accurate data capture of events as they occur during the trial

What should the Safety Plan Contain?- 2

Rigorous ascertainment of safety outcomes is essential and efforts to minimize missing data must be in place.

Document real reasons for missing data and analytic approaches to missing data

Ensure follow-up of all subjects for the intended period of the study especially for AESI or SAE (mortality) until resolution even if subjects discontinue study drug.

If a trial may stop early for efficacy, how will the sponsor ensure that there is adequate information to support the safety of the drug

Describe the statistical analyses to be conducted including sensitivity analyses

Types of Safety Studies

Small focused safety studies - special population studies

Example 1: Goal is to determine whether there is any prolongation effect of the drug on the QT interval: Issue is to decide on a meaningful endpoint - change from baseline, etc. Analysis plan- Summarize the current experience with the drug: pre-clinical, HERG studies, phase 2 clinical studies, decide on the number of baselines and time points at which to obtain follow-up ECGs simultaneously with drug concentration among elderly subjects with pre-existing CVD.

Example 2: Visual impairment induced by an antibiotic: One wants to know whether the event is dose related, time of onset, how long does it last, it is reversible, to what extent does it affect activities of daily living (driving a car, operating machinery, unable to feed ambulate), have a specific algorithm for patient follow-up including an examination by an ophthalmologist.

Types of Safety Studies - 2

Single cohort studies - informative if idiosyncratic reactions surface (e.g., drug induced hepatitis)

Controlled phase, efficacy declared, followed by an open-label phase

Controlled studies of adequate duration: easier to interpret in lieu of background rates, helpful if one wishes to “garner a safety claim”

Large simple safety studies - require careful execution and should be done in a usual care real-world setting

Inadequate Data Collection

Poorly designed data collection forms leads to data that are not useful although costly to obtain

Incomplete data: time of occurrence, severity, the final status of the patient after experiencing an adverse event are not always provided

Differences in culture and health care delivery systems result in differences in AE frequency and management (US data not necessarily superior to foreign data)

Inconsistent/inappropriate coding of adverse events

Database not easily accessible to construct patient time course during the trial

Database Issues

Unique patient identifier is “required”

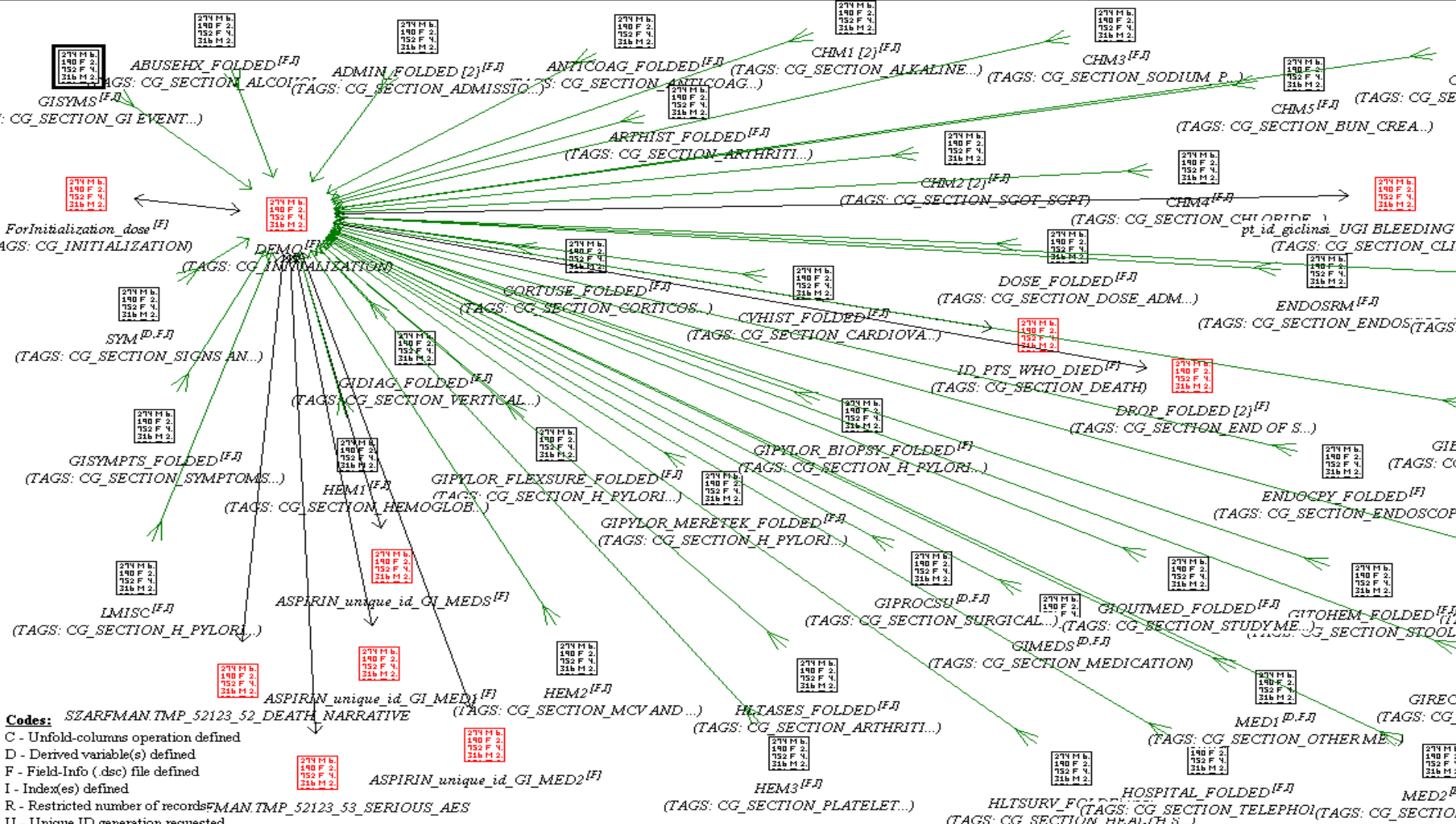
Data structure needs to be fully described and provide all AEs whether or not they occur at planned visits

AEs that occur after the “end of study” (**within some reasonable time interval after end of study**) may be important and should be included in the database.

Statisticians would like analysis data sets to facilitate review. There are standards being developed (CDISC, PhRMA).

Providing an errata report does improve the efficiency of reviews and minimize the number of requests to sponsor

We want to easily visualize the time course of events for each patient in the trial. (There are patient profile tools available.) The following slide is provided by: Ana Szarfman, MD (FDA).



Codes: SZARFMAN.TMP_52123_52_DEATH_NARRATIVE
 C - Unfold-columns operation defined
 D - Derived variable(s) defined
 F - Field-Info (.dsc) file defined
 I - Index(es) defined
 R - Restricted number of records
 U - Unique ID generation requested

OK

Verify

Cancel

V. Information Synthesis

Pooling of patient-level data from several studies is done to utilize larger sample size to provide opportunities to detect safety signals and is best if pre-specified

What to pool: controlled with controlled, do not include phase I PK/PD studies

Studies to be included should have similar methods of ascertainment of safety endpoints

Careful scrutiny of studies with zero AESI need to occur

Subgroup analysis: age, race, gender, geography, concomitant drug, concomitant disease, subgroups relevant to indication (neonatal, infants, older children)

Pooled analysis may show clinical heterogeneity -- needs further exploration

IV. Temporal Relations between Exposure and Adverse Experiences

Temporal exposure is one of the tenets of causality and is often overlooked in aggregate safety analysis

Provide clues to causality, adaptation and tolerance

Depletion of susceptible patients can potentially confound time-to-event analyses

Description of risk as a function of exposure, time since initial exposure, time to resolution, final outcome following an adverse experience, number at risk of must be accounted for (denominator)

Consider person-time (constant hazard), life-table, Kaplan-Meier, Log rank methods, or Cox PH Model

Reduce the domains of ADR by leveraging prior knowledge of similar compounds/class, PK/PD, dose effects, metabolic and host factors to guide study design and analysis

Metrics of Risk

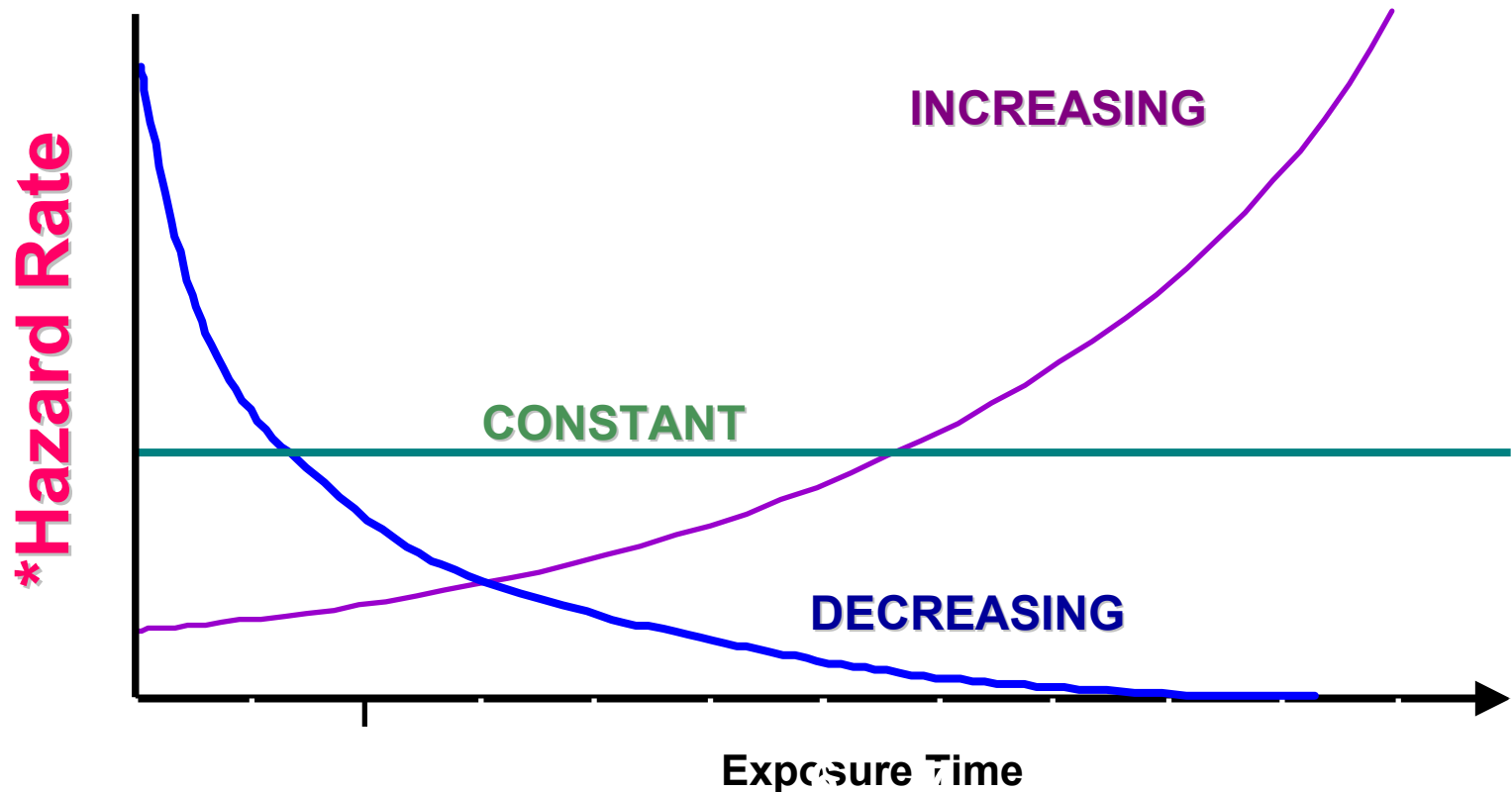
Crude rate $R = X / N$

Accounting for **differential exposure** - chronically administered drugs may demonstrate different AE profiles over time

Analyses that ignore time effects may fail to show important differences among treatments

The hazard may be constant (independent of time), decreasing, increasing, or show variant patterns

Hazard Functions for Three Patterns of Drug-Induced Clinical Events



* HR = RISK PER UNIT TIME

(O'Neill RT 1988)

Risks may be Time Dependent

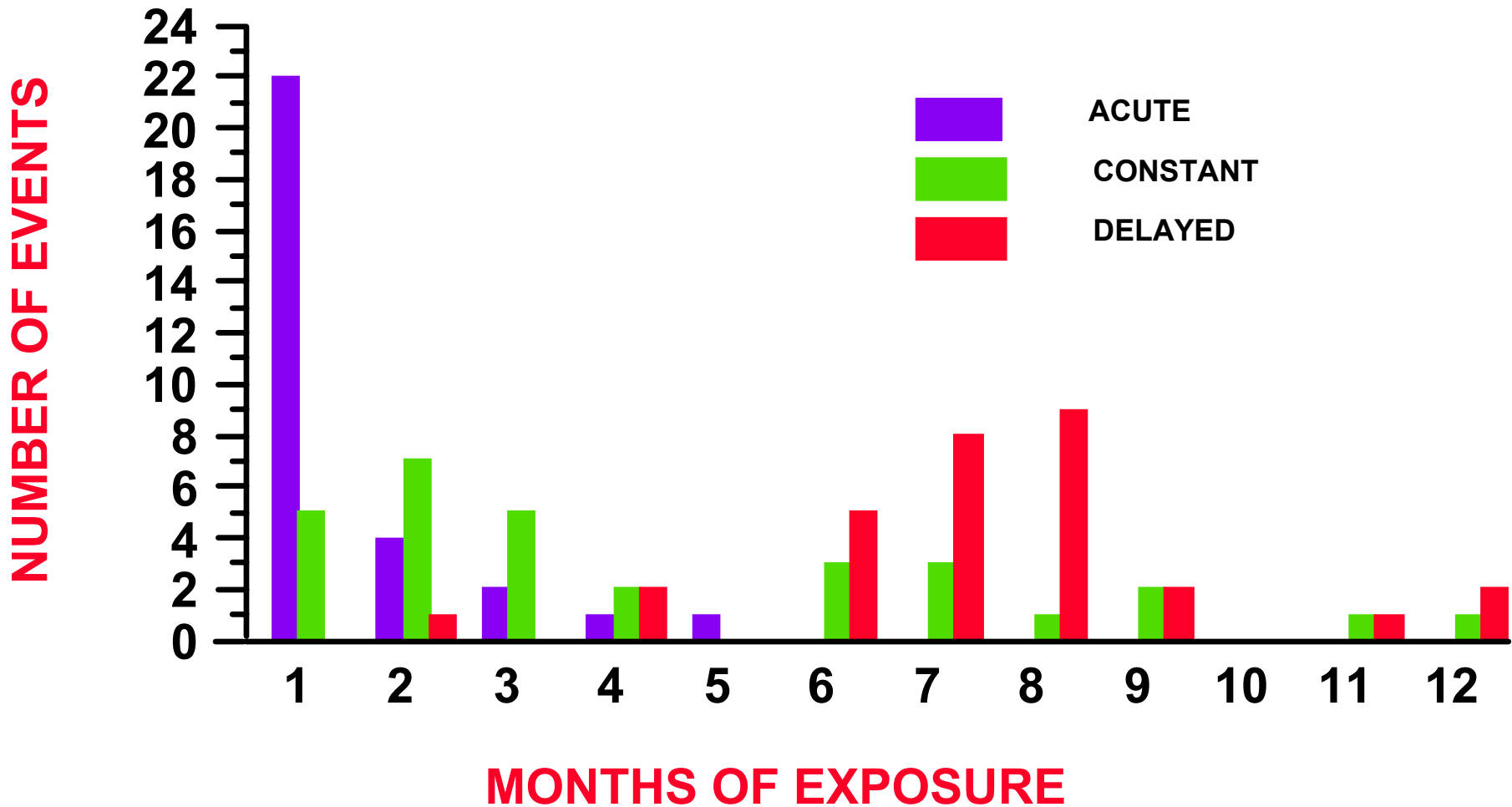
$$RR(t) = I(T; t) / I(C; t)$$

Where (I= incidence, T = treated, C = controls)

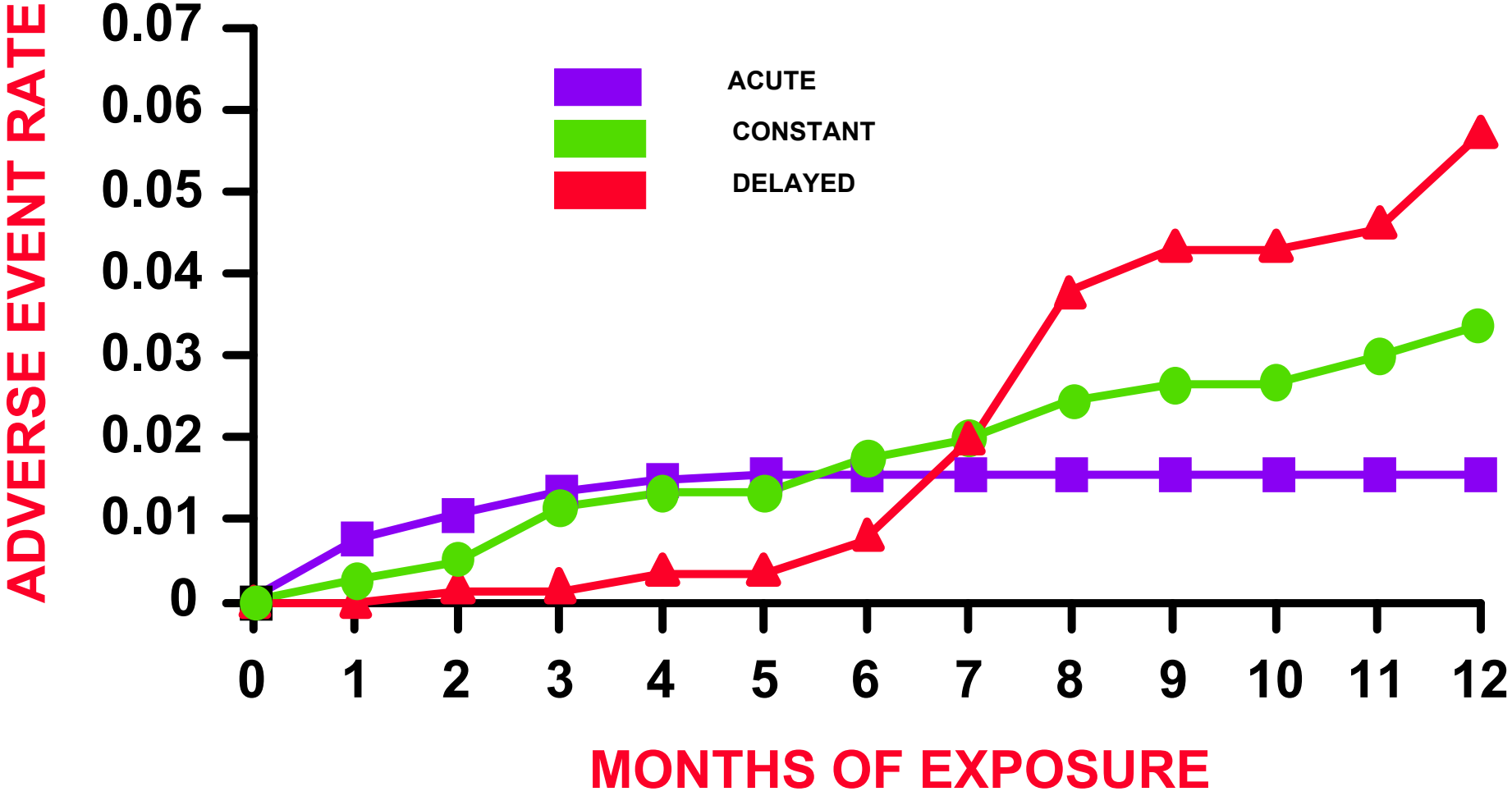
RR and RR (t) are not the same and need to be evaluated

This point is critical when combining relative risk estimates from different studies

Occurrence of Selected Adverse Events: Three Different Patterns



Estimated Cumulative Adverse Events Rates: Three Distinct Patterns of Occurrence



Cumulative versus Crude Adverse Event Rates from Two Trials

Study	Measure	Months Of Exposure			
		1	2	3	4
1	No. of Events	5	5		
	No. At Risk	500	150		
	Cumulative Rate	0.01	0.04		
	Crude Rate	$10/500=0.02$			
2	No. of Events	6	8	4	4
	No. At Risk	600	300	100	48
	Cumulative Rate	0.01	0.04	0.08	0.16
	Crude Rate	$22/600=0.04$			

A Simple Analysis Combining AE Rates from Two Trials: Utilizing Time Information

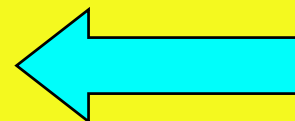
Combined Analysis

Months Of Exposure

	1	2	3	4
No. of Events	11	13	4	4
No. At Risk	1100	450	100	48
Cumulative Rate	0.01	0.04	0.08	0.16

Crude Rate

$32/1100=0.03$



Guidances

Three draft guidances listed below (CDER & CBER) to be published in the CFR for 90 days comment period

READY!!

1. Pre-marketing Risk Assessment
2. Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
3. Risk Management Programs

<http://www.fda.gov/cder/guidance/index.htm>

Risk evaluation is a continuum: draft guidances separate at this point for convenience of writing (these are interrelated concepts) and should be viewed as such

Future Guidances

Guidance to Clinical Reviewers on Conducting the Review of Safety (new version in progress)

Future Guidances: Office of Biostatistics

1. Guidance on “Statistical Principles Relevant to the Assessment of Pre-Marketing Safety”
2. MAPP for Statistical Review of Safety” relevant to the Review of Study Protocols and Review of NDAs

Office of Biostatistics has dedicated resources to the statistical review of safety. Statisticians and clinical reviewers working closely on these efforts to provide consistency across reviewing divisions.

Encourage collaboration between INDUSTRY and FDA

Future IND and NDA Submissions

Fully developed safety analysis plan which provides details on what data will be collected etc. especially for AESIs

Discuss approaches to missing data, what sensitivity analyses you plan to perform, how you will summarize the results, what subgroups are to be analyzed, etc.

Certainly, **one size does not fit all** so there needs to be communication with statistical and clinical reviewers regarding the adequacy of the safety analysis plan.

VI. Summary

Capitalize on sequential learning during drug development and formulate a safety analysis plan early.

Communicate with reviewing division for specific guidance at critical milestones and obtain advice on reasonable approaches to follow.

Sponsors are responsible for their products and this responsibility cannot be transferred or ignored.

Encourage the Industry and FDA to collaborate on ways to move the process forward as we refine our thinking, develop methodology and tools for safety analysis. It is necessary for the FDA to develop strategies of continuous improvement to ensure that the principles put forward actually achieve the intended purposes.

The regulatory bottom line is “protection of the public.”