# Planning and Development of Integrated Summaries of Safety

Miganush Stepanians, PhD
President & CEO
PROMETRIKA, LLC
Cambridge, MA

MBC

November 15, 2006

PROMETRIKA

# Outline

- Purpose of an Integrated Summary of Safety (ISS)
- Relevant Guidance Documents
- Members of the ISS Team
- The Planning Stage and the Key Planning Documents
- Practical Considerations for Biostatistics and Data Management

PROMETRIKA

# Purpose of ISS

- At the end of a development program for a drug product, sponsors are required to summarize the safety information from all clinical trials for submission with the marketing registration application.
- Analyses of integrated data from multiple studies are required to detect safety signals that may not be detected in individual trials.

# Guidance Documents

FDA: Guideline for the Format and Content of the Clinical and Statistical Sections of an Application, July 1988

- Goals of ISS are defined
- Minimum requirements for ISS are described:
  - Summary of the Clinical Studies
  - Extent of Treatment Exposure
  - Demographics and Background Characteristics
  - Adverse Events
  - Clinical Laboratory Assessments
  - Patient Narratives

# Guidance Documents (cont.)

FDA: Reviewer Guidance, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review, February 2005

- Assists FDA reviewers conducting the clinical safety reviews for NDAs and BLAs
- Identifies the critical presentations and analyses that reviewers expect in these applications, including illustrations of tables and graphs
- Discusses special cases and potential difficulties with integrated analyses

# Guidance Documents (cont.)

ICH: M4, The Common Technical Document, Implemented July 2003

- For US submissions in the CTD or eCTD format, integrated analyses of safety are still required.
- In a CTD or eCTD, the ISS should be placed in Module 5, section 5.3.5.3.
- If the narrative portions of the ISS are suitable for use in Module 2 (section 2.7.4 of the CTD), then they should be included there and referenced in Module 5, section 5.3.5.3.

# The ISS Team

The ISS Team is composed of the following professionals:

- Regulatory Affairs Strategists
- Medical Personnel
- **Biostatisticians and SAS Programmers**
- **Data Managers and Database Programmers**
- Medical Writers
- Regulatory Operations/Submissions Specialists

# The Planning Stage

Conducted by the entire team

1. Take stock of the studies in the program
2. Devise the macro strategy based on:
   - Clinical considerations
   - Availability of data
3. Draft the 2 key planning documents:
   - Integrated Data Dictionary
   - Statistical Analysis Plan (ISS SAP)

PROMETRIKA

# Integrated Data Dictionary

- Describes the structure of the integrated database for the clinical trials included in the submission
- The integrated data dictionary maps each variable from the individual study datasets to the integrated database
- Specifications include:
  - Variable names
  - Variable types, formats, labels
  - Codes and decodes for categorical and ordinal variables
  - Units and scales for continuous variables

PROMETRIKA

# Integrated Data Dictionary (cont.)

- **Structure of integrated datasets depend on:**
  - Structure of individual study datasets
  - Current standards expected by regulatory agencies, specifically CDISC
- **When is an Integrated Data Dictionary needed?**
  - Whenever files that do not have identical data structures are to be combined
  - To restructure existing integrated datasets to conform with CDISC requirements

PROMETRIKA

# Integrated Data Dictionary (cont.)

**How is the integrated structure determined?**

- For variables that are common to files across studies (e.g. all Phase II and III controlled studies):
  - Determine the most common definition of the variable
  - Convert variables in all files to be consistent with the "majority"

  Example: Weight is in kg in 4 of 6 trials. Therefore, convert weight from lb to kg in other two studies.

PROMETRIKA

# Integrated Data Dictionary (cont.)

- For categorical or ordinal variables that are common to files across studies:
  - Map code lists of categorical or ordinal variables into a common standard

Example: AE relationship to study drug

| Study 1 | Study 2 | Study 3 | Integrated |
|---|---|---|---|
| No | Unlikely | None | None |
| Yes | Possible | Possible | Possible |
| | Probable | Definite | Probable |
| | | | Definite |

PROMETRIKA

# Integrated Data Dictionary (cont.)

- Exclude variables that are in too few studies to be usable in integrated analyses.
- Consider converting to CDISC structure, if available for the particular domain (e.g., AE, Vitals, Labs, ECG).

  reference: www.cdisc.org

  Example: Current structure for vital signs - 1 record per subject per visit

| PTNO | DATE | SYSBP mm Hg | DIABP mm Hg | PULSE bpm | TEMP °C |
|---|---|---|---|---|---|
| 1005 | 23MAY06 | 110 | 80 | 72 | 38 |

PROMETRIKA

# Integrated Data Dictionary (cont.)

CDISC structure for vital signs – 1 record per test

Standardized Domain Name (VS) and Variable Names

| SUBJID | VSDTM | VSTESTCD | VSSTRESN | VSSTRESU |
|---|---|---|---|---|
| 1005 | 2006-05-23 | SYSBP | 110 | mm Hg |
| 1005 | 2006-05-23 | DIABP | 80 | mm Hg |
| 1005 | 2006-05-23 | PULSE | 72 | bpm |
| 1005 | 2006-05-23 | TEMP | 38 | °C |

PROMETRIKA

# Integrated Data Dictionary (cont.)

**Advantages of Submitting Integrated Datasets in CDISC Study Data Tabulation Model (SDTM) Format**

- Data structures are pre-defined
- Programming of integrated analyses can be standardized across programs
- FDA will spend less time reviewing application!!!
  - Little or no time needed to gain familiarity with data
  - Standardized tools are used to store, display, and analyze the data
- Although not mandatory currently, CDISC is likely to become a requirement

PROMETRIKA

# ISS Statistical Analysis Plan

- Similar to SAPs for individual studies, ISS SAPs detail the methods and analysis rules used in programming integrated tables.
- Table shells, list of figures, and any specialized safety listings should be included.
- Unlike SAPs for individual studies, the ISS SAP is usually written post-hoc, after study database locks and respective treatment unblindings have occurred.
- It is highly recommended that the ISS SAP be submitted to FDA for their “buy-in” and be discussed in the Pre-NDA meeting (similar with EMEA).

PROMETRIKA

# Special Analysis Issues

## Defining ISS Analysis Sets

- Will data for all patients exposed to study drug be integrated or will there be study groupings?
- In most cases, short-term (usually crossover) PK/PD studies in healthy volunteers are not combined with Phase II and Phase III studies in patients.
- Other possible study groupings:
  - Placebo-controlled trials vs. uncontrolled or active-controlled trials
  - Long-term trials vs. those of shorter duration

PROMETRIKA

# Special Analysis Issues (cont.)

**Defining the Patient Subsets of Interest**

- As a minimum, analyses by age group, gender, and race are always included.
- Other patient subsets may be required such as subsets by disease type (e.g., patients with indoor allergies versus outdoor allergies).

# Special Analysis Issues (cont.)

**Defining ISS Analysis Treatment Groups**

- Several questions arise, such as the following:
  - Should patients that dosed BID be combined with patients that dosed QD, if their total daily dose was the same?
  - Should patients that were allowed to titrate their dose be combined with patients that followed a specific dosing regimen?
  - Should data from studies that used slightly different drug formulations be combined?

PROMETRIKA

# Special Analysis Issues (cont.)

**Defining ISS Analysis Treatment Groups (cont.)**

- In addition to the various active dose groups, it is fairly common to combine placebo groups matching to different dosing regimens into a single group.
- It is also common to have an “all dose groups” category combining various doses of the drug.

PROMETRIKA

# Special Analysis Issues (cont.)

## Assigning Patients to Treatment Groups

- How are patients in crossover trials assigned? Generally, patient will be assigned to each dose group to which he/she was exposed.
- Studies with placebo run-in periods or open-label extensions lead to similar issues, where patients may be exposed to more than one treatment.
- These solutions are far from ideal, since the same patient is being counted multiple times in the denominators of the ISS treatment groups. Hence, the treatment groups are not independent.

PROMETRIKA

# Analysis of Adverse Events

- Must define treatment-emergent adverse events (TEAE) consistently across studies. Specify the analysis rules used to identify TEAE when first dose date or AE onset date is missing.
- Specify the analysis rules for assigning AEs in crossover studies (e.g., an AE that occurs during washout between treatment periods 1 and 2).
- Stay consistent with individual study analyses as much as possible.
- Clearly specify all analysis rules in the ISS SAP, so regulatory agencies can provide input on the proposed approach ahead of time.

PROMETRIKA

# Analysis of Adverse Events (cont.)

## Coding of Adverse Events

- Are there older studies in the program that were coded in COSTART or WHOART that need to be recoded in MedDRA?
- For studies coded in MedDRA, was the same version of the dictionary used?
- For studies coded with the same dictionary, was there consistency in coding?
- Team must devise a clear strategy for recoding of AEs and ensuring coding consistency.
- Specify coding rules in ISS SAP or standalone document, and submit to the regulatory agency in advance.

PROMETRIKA

# Analysis of Adverse Events (cont.)

## Subsets of Adverse Events

- The most common of such analyses are integrated analyses of AEs by causality and severity.
- For programs with special safety concerns, a subset of AEs of interest may also be analyzed separately (e.g., AEs associated with liver toxicity or cardiac AEs).
- One way to separate such AEs is to use the Standardized MedDRA Queries (SMQs) which go across SOCs to identify all events of potential interest.

# Analysis of Lab Data

**Types of Lab Analyses**

- Analyses focused on mean or median changes from baseline across treatment groups
- Analyses focused on outliers or shifts from normal to abnormal
- Listings of patients with extreme changes from baseline
- Analyses are intended to be descriptive only

PROMETRIKA

# Analysis of Lab Data

## Some Lab Analysis Issues

- What cut-points should be used to identify abnormally low and abnormally high values and outliers (e.g., CTCAE)?
- Should results from unscheduled lab tests and re-tests be included (not specific to integrated analyses)?
- Should data from open-label studies be analyzed separately in order to assess late-developing abnormalities, since placebo- controlled trials are generally short-term?

PROMETRIKA

# Summary

- It is important to have a Team approach with all key disciplines represented and meeting and communicating on a regular basis.
- Plan ahead to the extent possible: it is of course ideal to plan an ISS when designing the actual studies but even for programs with legacy data it is crucial to start the planning process as soon as the decision to submit is reached.
- Use the two key planning documents as tools to clearly specify all team decisions regarding data integration and analyses.

# Summary (cont.)

- Present the planning documents (especially the SAP) to the regulatory agencies and obtain their input before implementation.
- Deviations from the plan are inevitable because all issues cannot be foreseen: document all deviations clearly and completely for inclusion in the final ISS in the CTD.

# Contact

Miganush Stepanians, PhD

PROMETRIKA, LLC

725 Concord Avenue

Cambridge, MA 02138

617-868-2020 ext. 211

mstepanians@prometrika.com