Comprehensive Adoption Strategy for the FDA Standard Safety Tables and Figures

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Meet the Speaker

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- *The authors have no real or apparent conflicts of interest to report.*

Agenda

1. Overview of Standard Safety Tables and Figures: Integrated Guide (ST&F IG)
2. Gap Analysis
3. Benefits/Challenges of Adopting ST&F IG
4. Adoption Strategy
5. Conclusion

Overview of Standard Safety Tables and Figures: Integrated Guide (ST&F IG)

Overview of the ST&F IG

STANDARD SAFETY TABLES AND FIGURES:

INTEGRATED GUIDE

Center for Drug Evaluation and Research (CDER)

Biomedical Informatics and Regulatory Review Science (BIRRS) Team

- Version Date: August 2022
- https://www.regulations.gov/document/FDA-2022-N-1961-0046

Overview of the ST&F IG

Three sections (60 tables, 35 figures):

- Standard safety tables and figures (Core)
- Standard expanded safety tables and figures (Expanded)
- Optional safety tables and figures (Optional)

Overview of the ST&F IG

Standard Safety Tables and Figures

- General (general information regarding the clinical trial(s) submitted to support the application, demographic, disposition, and duration of exposure tables. Outputs presented by pooled analyses also should be generated for individual registration trials)
- Adverse Events Analysis
- Subgroup Analyses by Baseline Characteristics
- Laboratory Analyses
- Vital Signs

Overview of the ST&F IG

Standard Expanded Safety Tables and Figures

- Expanded Adverse Event Analyses
- Expanded Laboratory Analyses

Optional Safety Tables and Figures

- Optional Adverse Event Analyses
- Optional Laboratory and Vital Sign Data Distribution Over Time Figures

Overview of the ST&F IG

FDA FMQ Master file (FDA-2022-N-1961-0001_attachment_1.xlsm)

	FMQ NAME	FIRST PUBLISHED	LAST UPDATED	SYSTEM ORGAN CLASS
2	Abdominal Pain	v1.0	v2.1	Gastrointestinal disorders
3	Abnormal Uterine Bleeding	v1.0	v2.1	Reproductive system and breast disorders
4	Acute Coronary Syndrome	v1.0	v2.0	Cardiac disorders
5	Acute Kidney Injury	v1.0	v2.0	Renal and urinary disorders
6	Alopecia	v1.0	v2.1	Skin and subcutaneous tissue disorders
7	Amenorrhea	v1.0	v2.1	Reproductive system and breast disorders
8	Anaphylactic Reaction	v1.0	v1.0	Immune system disorders
9	Anemia	v1.0	v2.1	Blood and lymphatic system disorders
10	Angioedema	v1.0	v1.0	Immune system disorders
11	Anxiety	v1.0	v2.1	Psychiatric disorders
12	Arrhythmia	v1.0	v2.1	Cardiac disorders
13	Arthralgia	v1.0	v2.1	Musculoskeletal and connective tissue disorders
14	Arthritis	v1.0	v2.1	Musculoskeletal and connective tissue disorders
15	Back Pain	v1.0	v2.1	Musculoskeletal and connective tissue disorders
16	Bacterial Infection	v2.0	v2.1	Infections and infestations

Table of Contents | FMQ References | Instructions | Consolidated_List | Abdominal Pain | Abnormal Uterine Bleeding | Acute Coronary Sy ...

Overview of the ST&F IG

The purpose of standard safety tables and figures in ST&F IG is to provide a standardized set of safety analytic tables and figures that can be used by reviewers to interpret and conduct their review of clinical trial data. These tables and figures help to provide a clear and consistent presentation of safety data, allowing for easier comparison and analysis across different studies. They also serve as a reference for reviewers to identify safety signals and request custom analyses if needed.

Gap Analysis

Gap Analysis

Company internal standards vs ST&F IG

- FDA Medical Query (FMQ) related analysis
- Drug-Induced Liver Injury Screening Analyses
- Figures for Lab data and vital sign
- Risk difference (95% CI) on incidence accounting tables in standard ST&F doc that are not part of company standards
- Formatting differences

Benefits/Challenges for Adopting ST&F IG

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Benefits

- Standardization
- Improved Review Process
- Enhanced Safety Signal Detection
- Increased Transparency
- Facilitates Regulatory Compliance
- Efficiency and high quality

Challenges

- Updates to company internal standards
- Legacy studies vs. ongoing studies
- Industrial requirements and guidance
- Training and awareness

Adoption Strategy

Adoption Strategy

After reviewing benefits and challenges, we proposed strategy for adopting ST&F IG:

- Ensure consistency with industry guidelines
- Consider existing company standard reports and available resources
- Focus on the adoption of the guideline. ST&F serves as a framework. Focus on contents. Create tools for the reports that don’t exist in company library first
- The strategy consists of five phases, each addressing specific aspects of the adoption process

Phase I: Awareness, Guide on Creating FMQ Datasets

- The FMQs (FDA Medical Query) are standardized groupings of related preferred terms (PTs), categorized as either narrow or broad, that have been developed by FDA reviewers to facilitate safety signal detection
- 19 out of 60 FDA mockup tables are FMQ related analysis
- FMQ has different usage as SMQ (Standardized MedDRA Queries) and CQ (Customized Queries), as a result, the dataset structure for FMQ is different from SMQ /CQ
- Several companies received FDA requests to submit FMQ related analysis although this is a draft guide

Phase I: Awareness, Guide on Creating FMQ Datasets

- Align with the leadership on the adoption strategy and secure resources for development
- Collaboration with other pharmaceutical companies
  - FDA safety PHUSE breakout meeting
- Collaboration with the CDISC ADaM team to create CDISC ADaM knowledge papers
  - Provide examples for handling FMQ analysis datasets
  - Plan for public review by end of 2024
- Create awareness among stakeholders about the FMQ datasets
  - Educating stakeholders about FMQ and providing them with the necessary tools and resources to effectively create FMQ analysis datasets

Phase II: Develop ADaM Template Programs/Standard Reporting Macros for FMQ Analysis

- FMQ related analysis does not exist in current standard reporting macros
- As mentioned earlier, 19 out of 60 standard mockup tables are FMQ related analyses
- Develop ADaM SPEC (ADAEFMQ/ADALGFMQ)
  - The details about FMQ analysis datasets will be presented in the next two papers
- Develop ADAEFMQ/ADALGFMQ creation program template
- Develop standard reporting macros for 19 FMQ related tables

Phase II: Develop ADaM Template Programs/Standard Reporting Macros for FMQ Analysis

In the second phase, ADaM template programs and reporting macros are developed for FMQ analysis. This step ensures that the analysis of FMQ data is standardized and consistent across different projects and teams. By providing a set of standard programs and macros, this phase promotes efficiency and follows ST&F IG for FMQ analysis.

Phase III: Update ADDILI and DILI Reports

- DILI: Drug-Induced Liver Injury
- Screening analyses to detect a potential signal for DILI (e.g., Hy's Law, cholestasis, or Temple's Corollary quadrants)
- Hy's Law
  1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST
  2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
  3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury
- The presence of even one or two Hy's Law cases may be sufficient to jeopardize drug approval or raise concerns for post marketing safety

Phase III: Update ADDILI and DILI Reports

- Our company has standard macros for DILI reports
- The standard reporting macros were developed based on ‘Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation’, Released in 2009
  - Hy’s law was determined from lab data collected within the same day

Phase III: Update ADDILI and DILI Reports

- Recently, FDA released several guidelines related to DILI using different criteria
  - ‘Standard Safety Tables and Figures’, 2022
  - ‘Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Nonalcoholic Steatohepatitis (NASH)’, 2021
  - Instead of using lab observations from the same day, the new method uses the maximum values from postbaseline to evaluate DILI (using maximum treatment-emergency liver test abnormalities)

Phase III: Update ADDILI and DILI Reports

- The new method has greater power to detect a potential DILI signal (e.g., cases in the Hy's Law, cholestasis, or Temple's Corollary quadrants)
- For this reason, we need to adopt new FDA guidelines to report DILI and update current standards for DILI reports
- CDISC ADaM DILI team is working on creating ADaM examples document. We will work with this team and contribute to this project
- The details will be presented in "Designing an ADaM Dataset for Streamlined Drug-Induced Liver Injury Screening Analyses"

Phase III: Update ADDILI and DILI Reports

- Phase III focuses on updating ADDILI and the DILI reports. This includes adopting new FDA guideline for reporting DILI, ensuring that the reports are accurate and in line with the latest regulatory requirements
- This phase is crucial in improving the quality and consistency of DILI reporting

Phase IV: Create Macros for Reports/Graphs not Covered by Current Standard Library

- Create additional standard reporting and graphic macros for the tables and figures in the ST&F IG that are not covered by the current company standard macro library. This phase aims to ensure standard tools are available to produce all tables and figures in ST&F
- Enhance the reporting capabilities and ensures that they are in line with industry best practices

Phase V: Future Enhancements and Updates

- Phase V is yet to be determined and will be developed based on the evolving FDA needs and feedback from the stakeholders, and PHUSE recommendation regarding ST&F IG
- May update existing macros to produce tables and figures that are fully compliant with the ST&F IG
- Ensures continuous improvement and adaptation to future requirements

Conclusion

Conclusion

- The ST&F adoption plan presented in this paper is a comprehensive strategy aimed at increasing awareness and utilization of the FDA ST&F

- The plan consists of five phases addressing specific aspects of the adoption process
  - based on a thorough gap analysis,
  - aligned with CDISC guidelines
  - emphasizing consistency with industry best practices

- By following this adoption plan, pharmaceutical companies and CROs can effectively implement the FDA guidelines and improve the quality and consistency of safety analysis and reporting.

Acknowledgements

I would like to thank Susan Kramlik, Greg Zhou, Amy Gillespie, Suhas Sanjee, and Dan Feng Fu for the review and support.

Thank You!