Safety Review and the eCTD

Howard D. Chazin, MD, MBA

Acting Associate Director for Safety

FDA CDER Office of New Drugs

Outline

1. **What is a Safety Review?**
2. Guidance, Policy, GRPs and the Risk Assessment Guidances
3. Ongoing Confusion between the ISS and SCS
4. Challenges of Reviewing Electronic Documents
5. Specific Questions and Answers

How is Safety Defined?

- Reference in the FD&C Act interprets the "safety" of a drug as meaning that the benefits of a drug outweigh its risks for the uses recommended in labeling.

What is a Safety Review?

- Review staff evaluate marketing applications for efficacy and safety and consider benefit and risk.
- Reviewers expect to receive a complete application at the time of filing (exclusive of the 120 day safety update).
- Efficacy and safety reviews may be done by a single reviewer or split into separate reviewers, one for efficacy, one for safety.

Different Approaches:Safety vs. Efficacy

- Efficacy data
  - identify endpoints in advance
  - hypothesis testing
  - focus on individual studies
- Safety data
  - don’t know endpoints in advance (use broad screening and careful observation)
  - exploration and estimation
  - focus on pools of studies

Goals of the Safety Review

- Identify and assess adverse events reported in clinical trials
- Evaluate the adequacy of the applicant's safety data and testing
- Assess overall quality of the safety data within an application

Identify and Assess Adverse Events

- To identify and closely examine serious adverse events that suggest important problems with a drug-- specifically, adverse reactions severe enough to prevent its use altogether or require special risk management efforts

Identify and Assess Adverse Events

- To identify and estimate the frequency of the common (usually non-serious) adverse events that are, or may be, causally related to the use of the drug;
- To identify unresolved safety concerns that will need attention prior to approval or that should be assessed in the postmarketing period, including such concerns as the absence of data from high-risk populations or potential interactions

Consider Adequacy of Safety Data and Testing

- To consider the adequacy of the data available to support the safety analysis and to identity the limitations of those data.
  - At a minimum, this includes assessments of whether the extent of exposure at relevant doses is adequate
- To determine that all appropriate tests were performed
  - e.g., orthostatic blood pressure, relevant lab tests

Assess Overall Quality of an Application

- Does data agree across all sources?
  - CRF and narrative summaries
  - Data tables and data listings
- Have all the important issues been addressed?
  - Concerning safety signals have been explored and discussed
  - Class effects have been explored and discussed

Additional Goals of the Safety Review

- Identify factors that predict the occurrence of adverse reactions, including patient-related factors and drug-related factors
- Identify, where possible, ways to avoid adverse reactions (dosing, monitoring) and ways to manage them when they occur
- For a drug that is to be approved, provide a comprehensive evaluation of risk information adequate to support a factual and sufficient summary for product labeling.

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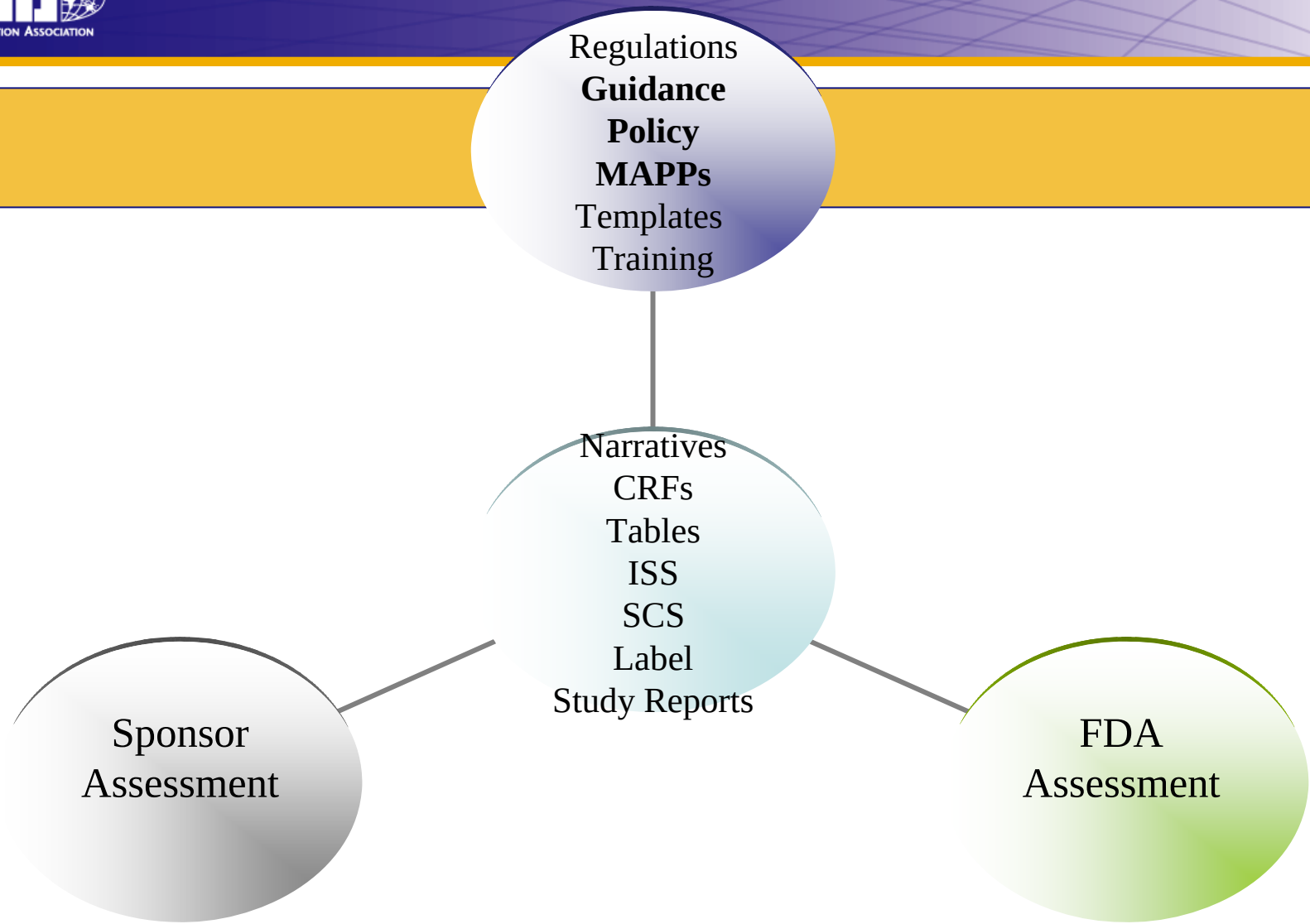
Regulations
Guidance
Policy
MAPPs
Templates
Training
Narratives
CRFs
Tables
ISS
SCS
Label
Study Reports
Sponsor Assessment
FDA Assessment

Guidance and Policy

- Sponsors need to be aware of various Guidances, MAPPs and Good Review Practices (GRPs) that the review staff utilize for safety review.
- Knowledge of these documents helps sponsors prepare better applications and better attend to review issues and expectations.

Guidance and Policy

- FDA Guidance: Format and Content of the Clinical and Statistical Sections of an Application (aka “Clin-Stat Guidance” 1988)
- ICH E3 Guideline for Industry E3: “Structure and Content of Clinical Study Reports” (1995)
- ICH M4-Common Technical Document for the Registration of Pharmaceuticals for Human Use (2001)
  - Standardized submissions across all regulatory organizations.
  - BUT the ISS and ISE are FDA specified documents, not addressed by M4!!

Good Review Practices to Know

http://www.fda.gov/cder/other/GRP.htm

- Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review
- Clinical Review Template MAPP
- NDA Filing Review Issues
- Premarket Risk Assessment

Good Review Practices (GRPs)

A Good Review Practice, or GRP, is a "documented best practice" within CDER that discusses any aspect related to the process, format, content and/or management of a product review. GRPs are:

- developed over time as superior practices based on experience, and provide consistency to the overall review process of new products
- developed to improve the quality of reviews and review management. GRPs improve efficiency, clarity, and transparency of the review process and review management
- adopted by review staff as standard processes through supervisor mentoring, implementation teams and formal training when necessary

As GRPs develop, review staff will adopt them into their daily review activities. Since GRPs can change and evolve frequently as a result of new science, statutes, regulations, guidances, and accumulated experience, the policies will be updated regularly.

Review staff are expected to follow GRPs and may depart from them only with appropriate justification and supervisory concurrence.

The GRP initiative is a true collaborative effort between many Offices within CDER. For additional information, please contact Lana Pauls (lana.pauls@fda.hhs.gov), Quality Management Staff (QMS) at (301) 443-5169.

General / Review Management

- Good Review Procedures (MaPP)

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- Good Review Procedures (MaPP)
- Good Review Management Principles and Practices (GRMPs) (Guidance)

Biometrics

- Biostatistics Biologics Licensing Application Review Template (MaPP)
- Biostatistics New Drug Application Review Template (MaPP)

Chemistry, Manufacturing and Controls

Clinical

- Consultative Review of Drugs Regulated Within OND (MaPP)
- Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (Guidance)
- Clinical Review Template (MaPP)
- NDA Filing Review Issues (MaPP)
- Premarket Risk Assessment (Guidance)
- Evaluating the Risks of Drug Exposure in Human Pregnancies (Guidance)
- Labeling for Human Prescription Drugs -- Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information (Guidance)

Clinical Pharmacology

- Clinical Pharmacology and Biopharmaceutics NDA Review Template (MaPP)
- Exposure Response Relationships- Study Design, Data Analysis and Regulatory Applications (Guidance)
- Integration of Study Results to Assess Concerns About Human Reproductive and Developmental Toxicities (draft) (Guidance)

Pharmacology/Toxicology

- Pharmacology/Toxicology Review Format (Guidance)

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3 Risk Assessment Guidances

- Premarket Risk Assessment Guidance
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment Guidance
- Development and Use of Risk Minimization Action Plans (RiskMAP) Guidance

Premarket Risk Assessment Guidance

- Generating risk information
  - What are the characteristics of an ideal safety database?
    - Controlled trials performed throughout
    - Diverse population (age, race/ethnicity, concomitant disease, drugs….)
    - Range of doses explored throughout development

Premarket Risk Assessment

- Analyzing and Presenting Risk Information
  - Grouping of adverse events
  - Temporal relations between adverse events and product exposure (time-to-event analyses)
  - Analyses of dose effects
  - Data pooling
  - Missing safety data
- Plea for improved quality of data submission
  - supporting documentation in CRF
  - complete narratives (with all pertinent info)

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Confusion about the SCS and the ISS

- “Do I need an ISS for this submission?”
- “What is the difference between the summary of clinical safety (SCS) and the integrated summary of safety (ISS)?”
- “Where does it all go?”

FDA Regulations Require Summaries AND Integrated Assessments

Table 1: ISE- and ISS-Related Sections with Corresponding Regulations

CTD Section	U.S. Regulation	Comment
2.5 Clinical Overview (~30 pages)		
2.5.3 Overview of Efficacy	N/A	Not a U.S. requirement, but recommended by ICH M4E
2.5.4 Overview of Safety		
2.7 Clinical Summary (~50 – 400 pages)		
2.7.3 Summary of Clinical Efficacy	21 CFR 314.50(c)(2)(viii)	U.S. requirement for a clinical summary
2.7.4 Summary of Clinical Safety		
5.3 Clinical Study Reports		
5.3.5.3 Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses)	21 CFR 314.50(d)(5)(v)	Integrated Summary of Effectiveness
	21 CFR 314.50(d)(5)(vi)	Integrated Summary of Safety

Draft Guidance published June 2007…

Guidance for Industry

Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document

DRAFT GUIDANCE

Module 2 Overview and Summary of Safety

- Section 2.5.4- Overview of Safety- should discuss study design, and general safety results-mostly text with some in-line tables and figures.
- Section 2.7.4 – Summary of Clinical Safety- summaries of data without all the details. Usually derived from the full ISS. Text, tables and figures only.
- All of Module 2 has a size limitation about 400 pages max!

Module 5- Location for ISS and ISE

- Specifically Section 5.3.5.3 – Integrated Analyses from More than One Study
- Module 5 was designed to contain more detailed in-depth analyses including text, but also large appendices of tables, figures and datasets.
- Module 5 has no space limitation

General Submission Organization

Module 2.7.4
Summary/SCS

Summary Text

Within text tables

different

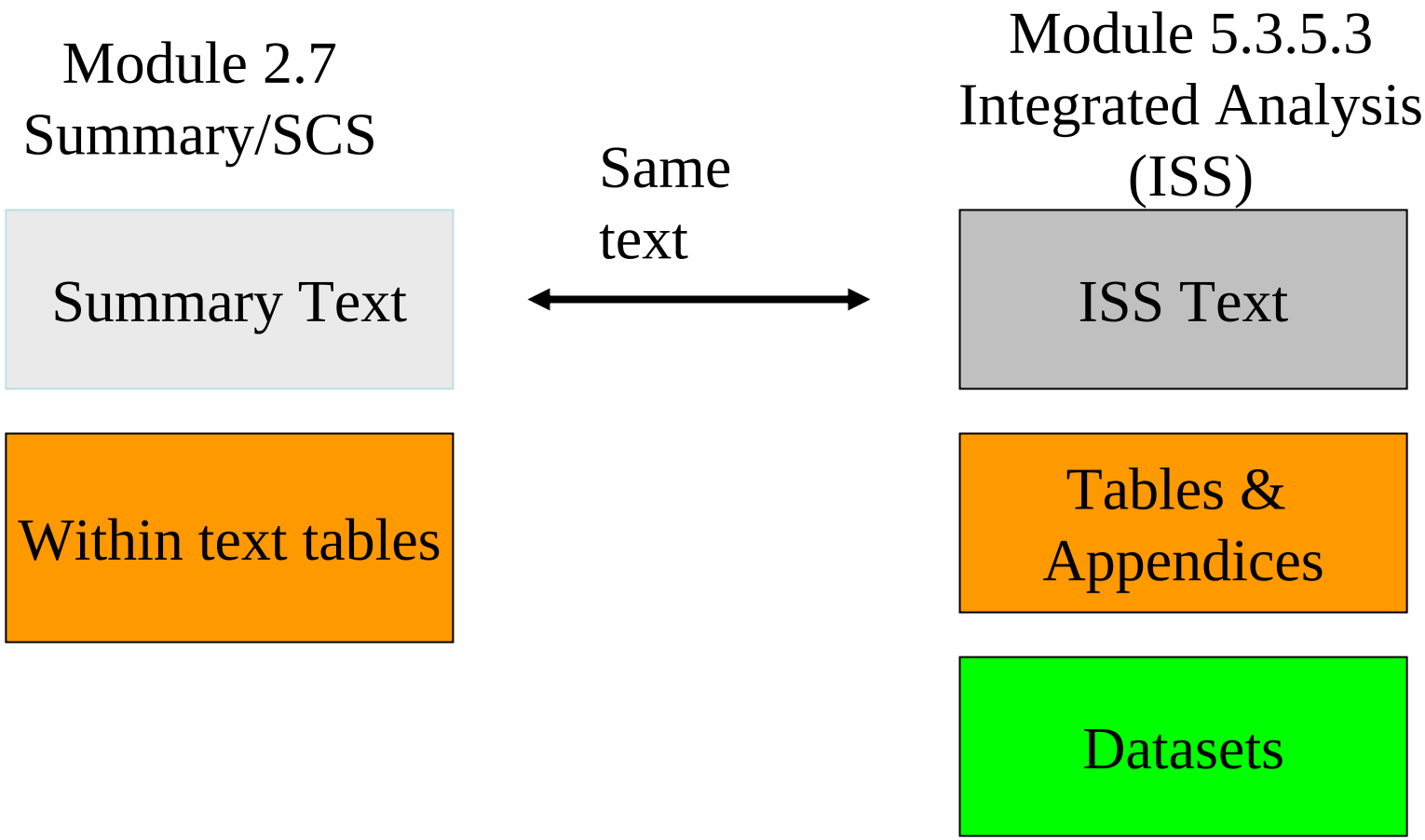
Module 5.3.5.3
Integrated Analysis
(ISS)

ISS Text

Tables &
Appendices

Datasets

Exception: Orphan Drug with Small Studies)



Exception- NDA Supplement with Small ISS

Module 2.7
Summary/SCS

Summary Text

Within text tables

different

Module 5.3.5.3
Integrated Analysis
(ISS)

refer reader to
SCS for text

Tables &
Appendices

Datasets

Not Acceptable-Possible Refuse to File Issue!

Module 2.7.4
Summary/SCS

Module 5.3.5.3
Integrated Analysis
(ISS)

SCS/ISS Text
Summary Text

Nothing
submitted!

Tables &
Appendices

Datasets

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Electronic Document Transition

- The FDA is transitioning to electronic documents for all submissions. Current new policy changes the format from eNDA to eCTD for submissions.
- The goal is to eventually achieve an all-electronic environment
- **Technical and cultural hurdles** along with a cultural shift in review staff continue to challenge this transition.

Examples of Technical Hurdles

- Difficult to know if a submission is complete in eCTD format due to subfolders.
- Narratives often not linked to CRF
- Links from ISS to narrative are on first page, rather than actual narrative.
- Datasets that are derived from other datasets cannot be reproduced.

Examples of Cultural Hurdles

- More experienced reviewers started with paper submissions, then eNDA and/or paper CTD, now eCTD.
- Not easy to read a submission on one screen and write a review using another screen.
- The nature of eCTD is that many windows can be open in the desktop and reviewers can be “electronically” knee-deep in data.

Measures to Improve the Transition

- **CDISC** format will help as standardized data will allow for use of data evaluation tools
- **Preview of the eCTD** by sponsors to review teams during filing period would help to orient staff
- Sponsors need to understand the analyses and expectations of review staff when reviewing submissions. (MAPPs, Guidances and templates)

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Electronic individual case safety reports ICSRs-

- Do not go in the NDA, they are sent to AERs.
- NOT to be submitted in duplicate to the NDA or to the eCTD.
- Preferred way to send these is through the E2B Gateway, electronically.

What about IND safety reports?

- Depending on severity, there is an initial phone call to FDA, then a written report due either 7 or 15 days post adverse event
- Unexpected fatal or life-threatening event- 7 calendar days
- Any adverse event that is serious and unexpected or animal tests that suggest significant risk-mutagenicity, teratogenicity, etc.- 15 calendar days

What about NDA safety reports?

- 15 day reports- SAEs go to AERs only and then a written update, also to AERs.
- Annual Report or PSUR- to the eCTD

FYI-Many Places for Safety Info in the eCTD

- Safety Information Amendment – 1.11.2
- Summary of Safety Info (Annual Report) – 1.13.3
- Overview of Safety – 2.5.5
- Summary of Clinical Safety – 2.7.4
- ISS/ISE 5.3.5.3 – variations may also show up in 2.7.4 or 2.7.3 with datasets and tables in 5.3.5.3
- Study report body, Module 5
- Clinical Data in Module 5 (Preclinical in Module 4) –ICH E3 format
- PSUR – (in lieu of the Postmarketing Periodic Adverse Experience Reports (21CFR314.80)) - 5.3.6.

Electronic Regulatory Submissions and Review

- Check the ERSR Website for all your info regarding electronic submissions:

- http://www.fda.gov/cder/regulatory/ersr/

Electronic Regulatory Submissions and Review

Welcome to the Center for Drug Evaluation and Research's Electronic Regulatory Submissions and Review (ERSR) web page. This page provides information about the electronic submission of regulatory information to the Center and the review of it by CDER staff. Additional guidance documents, when available in draft or final form, will be added to this page.

NOTICE: Click here for important instructions regarding electronic submissions, effective January 1, 2008.

Electronic Regulatory Submissions

- All CDER Guidances on Electronic Submissions
- General Considerations
- Abbreviated New Drug Applications (ANDAs)
- Annual Reports for New Drug Applications (NDAs)
- Carcinogenicity Data
- Providing Digital Electrocardiogram (ECG) Data
- Electronic Common Technical Document (eCTD)
- Drug Master File
- Investigational New Drug Applications (INDs)
- Launch Material and Other Submissions to the Division of Drug Marketing, Advertising, and Communications (DDMAC)

Thank You!