

Integrated Summary of Safety (ISS) Demystified: Practical Considerations for a Successful ISS

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Agenda

01 Aim of the Paper

02 ISS in Regulatory Submissions

03 ISS Content

04 ISS Planning

05 ISS Implementation

06 Conclusion

Aim of the Paper – Demystify ISS



Break down ISS
preparation to two
stages

Highlight key
considerations

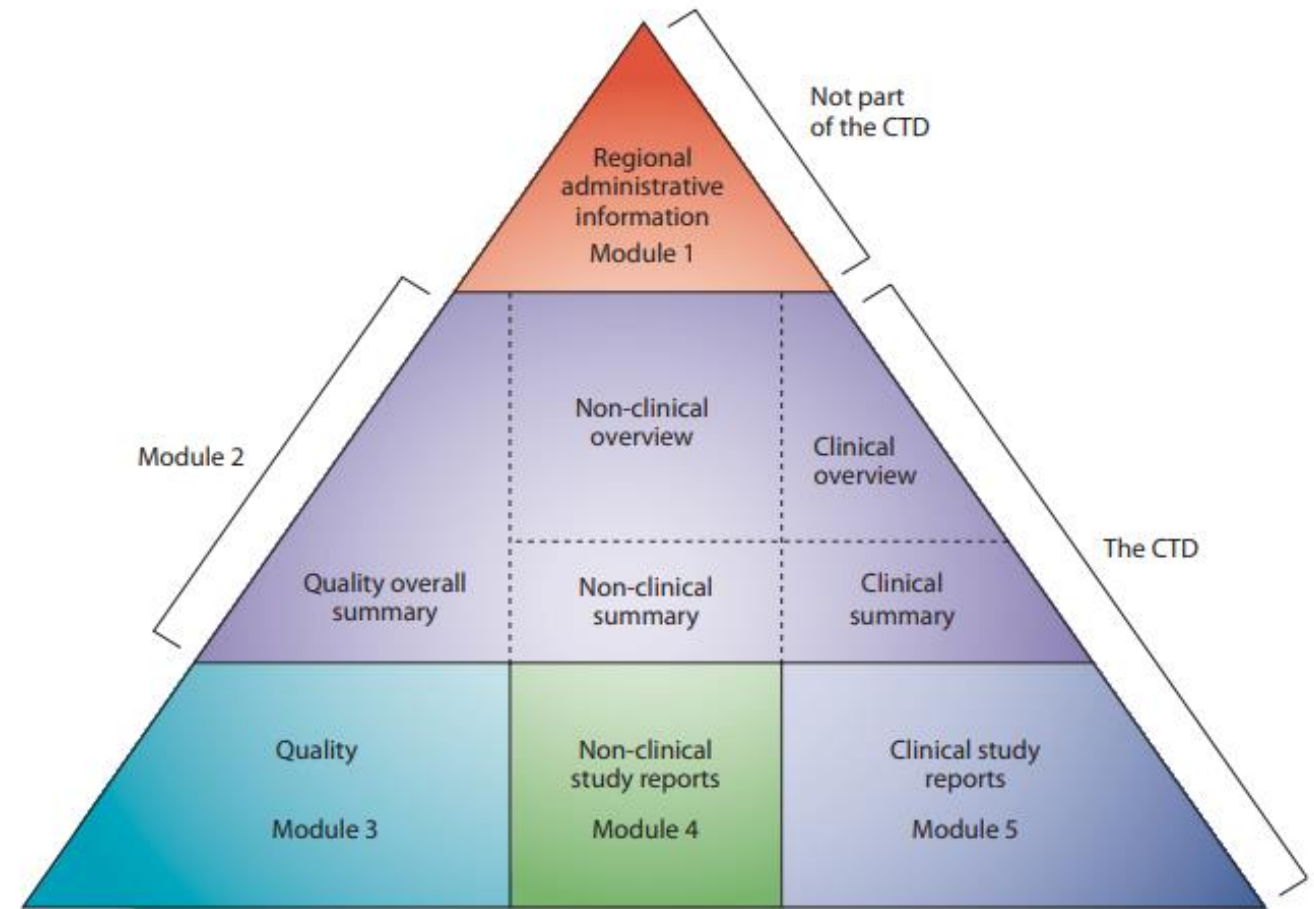
Use examples to
illustrate
recommendations

The background features abstract, overlapping shapes in teal, light blue, and pink. The teal shapes are angular and sharp, while the light blue and pink shapes are more rounded and organic. The text is centered over these shapes.

ISS in Regulatory Submissions

Common Technical Document Triangle

Source: ICH CTD overview page
<https://www.ich.org/page/ctd>



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

ISS Placement in FDA NDA

U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, April 2009. <https://www.fda.gov/media/75783/download>

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

CTD Section	U.S. Regulation	Comment
2.5 Clinical Overview (~30 pages) 2.5.4 Overview of Efficacy 2.5.5 Overview of Safety	N/A	Not a U.S. requirement, but recommended by ICH M4E
2.7 Clinical Summary (~50 – 400 pages) 2.7.3 Summary of Clinical Efficacy 2.7.4 Summary of Clinical Safety	21 CFR 314.50(c)(2)(viii)	U.S. requirement for a clinical summary
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) 21 CFR 314.50(d)(5)(vi)	Integrated Summary of Effectiveness Integrated Summary of Safety

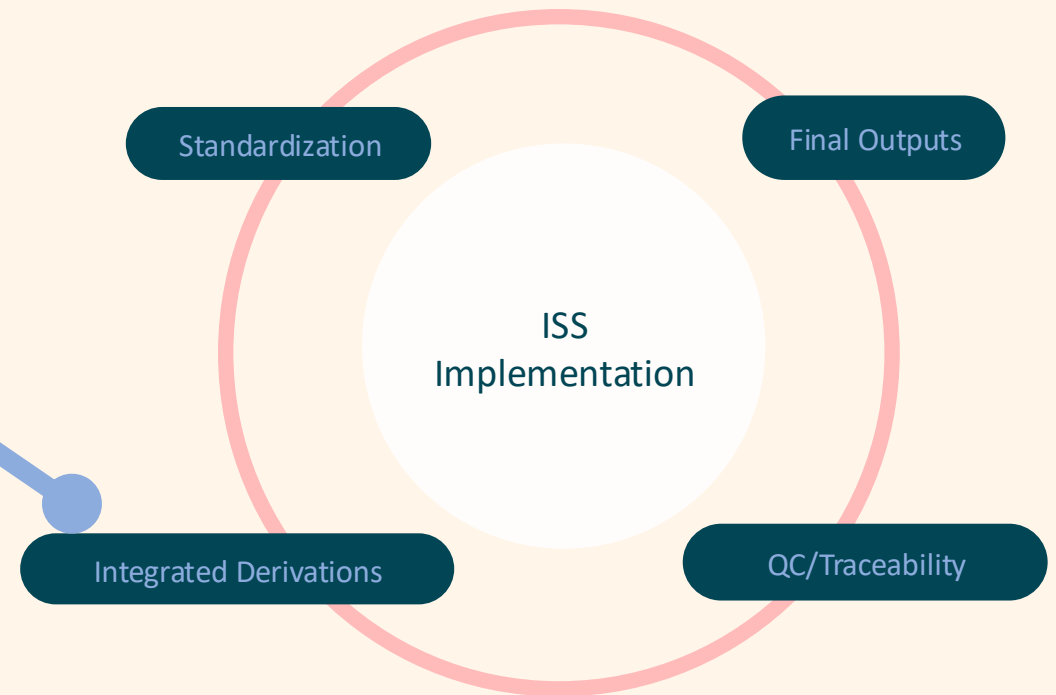
Content For ISS

FDA: Guideline for the Format and Content of the Clinical and Statistical Sections of an Application, July 1988.
<https://www.fda.gov/media/71436/download>

- Table of all investigations pertinent to safety
- Overall extent of exposure
- Demographic and other characteristics of the study population
- Adverse experiences in clinical trials
- Clinical laboratory evaluation
- Adverse events, including laboratory abnormalities, from sources other than clinical trials
- Animal data
- Analysis of dose-response information
- Drug-drug interactions
- Drug-demographic and drug-disease interactions
- Pharmacologic properties other than the property of principal interest
- Long-term adverse effects
- Withdrawal effects

ISS Blueprint

(Planning-to-Implementation Workflow)





ISS Planning

Objectives



Regulatory Objectives

- Submission Type
- Agency/Region
- Indication
- Target Population
- Regimen

Analysis Objectives

- Signal Detection
- Signal Clarification
- Signal Characterization
- Signal Communication

Study Selection

Indication / target population relevance.

Data collection consistency.

Indication	Study Phase	#	Population	Design/Dose Group	Duration [weeks]
A	Ph1	1	Adult	Open Label Low, Middle, High	4 Treatment + 44 Extension
A	Ph3	2	Adult	Randomized Middle + Active Comparator	52 Randomized Treatment
A	Ph3	3	Child (1-<18 yo)	Randomized Middle + Active Comparator → Both Arms Middle	52 Randomized Treatment + 52 Extension
A	Ph2	4	Child (1-<18 yo)	Open Label Middle	52 Treatment + x Weeks Extension
B	Ph1	5	Adult	Open Label Low, Middle, High	4 Treatment + 44 Extension
C	Ph1	6	Adult	Open Label Low, Middle, High	4 Treatment + 44 Extension
A	Investigator Sponsored	7	Child (1-<18 yo)	Open Label Low, Middle, High	4 Treatment + x Weeks Extension

Pooling Strategy

When one pooled database does not cover all the objectives, use tiered pool hierarchy

Anchor core pools to the intended submission use-case.

Separate controlled and uncontrolled evidence to protect interpretability.

Maintain traceability and consistent derivations across pools.

Pool ID	Pool name (short)	Primary objective(s) supported	Studies contributing	Dose focus	Period(s) included
P1	All-Exposed Program Pool (A+B)	Signal detection (broad screen); overall exposure context	1–5	All doses (Low/Middle/High)	All treatment + extensions
P2	A + Middle Dose Pool (Target-Use)	Characterization for target use, including long-term AE patterns by exposure duration, and subgroup analysis for pediatric safety characterization	1–4	Middle only (target dose)	All periods at Middle Dose (treatment + extension)
P3	Controlled A + Middle Pool	Signal clarification (comparative anchor)	2–3 (randomized periods)	Middle dose compared with active control	Randomized controlled periods only

P3 supports signal communication with comparative statements while P2 supports descriptively



ISS Implementation

Key Points

Standardization



Coding

- Adverse Events, Medical History (if included) -- MedDRA
- Prior/Concomitant Medication -- WHO Drug Dictionary
- Up-versioning/Re-coding
- Grouped Term Analysis in addition to PT: SMQ, CMQ

Test Data Comparability

- Unit
- Reference Ranges
- PCS Criteria

Integrated Derivation-TE Period & Normalizing Treatment Duration



Define “during
treatment”
consistently

Treatment
gap/dose change
management

TE period
boundary fit-for-
purpose

EAIR/EAER

Integrated Derivation- Aligning Visit Windows

- Define the ISS analysis-visit spine and the anchor for relative timing (e.g., first dose or period-specific first dose).
- Select an implementation method per domain/output: (i) derive ISS analysis visits directly using date-based windows (Method 1), or (ii) map study-native AVISIT/AVISITN to ISS Analysis Visits (Method 2).

Indication	Study Phase	#	Population	Design/Dose Group	Duration [weeks]	SOE
A	Ph1	1	Adult	Open Label Low, Middle, High	4 Treatment + 44 Extension	Day 8, W4, W8, W12, W24, W36, W48
A	Ph3	2	Adult	Randomized Middle + Active Comparator	52 Randomized Treatment	Day 8, W4, W8, W13, W26, W39, W52
A	Ph3	3	Child (1-<18 yo)	Randomized Middle + Active Comparator → Both Arms Middle	52 Randomized Treatment + x Extension	Day 8, W4, W8, W13, W26, W39, W52, W65, W78, W91, W104...
A	Ph2	4	Child (1-<18 yo)	Open Label Middle	52 Treatment + 52 Weeks Extension	Day 8, W4, W8, W26, W52, W78, W104
B	Ph1	5	Adult	Open Label Low, Middle, High	4 Treatment + 44 Extension	Day 8, W4, W8, W12, W24, W36, W48

Conclusion



Successful ISS development: a two-stage process, design and implementation.

We used a mock sample program for illustration.

Intended to provide a clear thought process for ISS planning

Highlighted a key set of implementation decisions that strongly influence interpretability, traceability, and reviewability.

Strengthen the ISS, enhance confidence in the safety evidence supporting the marketing applications, facilitate efficient regulatory review and decision making.



References

See Reference List in PHUSE US Connect 2026 Paper AS15



Thank you ! Questions?

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