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

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ABSTRACT

The ISS is a critical component of regulatory submissions to agencies worldwide. It provides a comprehensive view of a product's safety profile across clinical trials. A successful ISS requires strategic planning and unified execution. Key design-phase considerations include defining clear objectives, selecting studies with compatible populations and endpoints, and establishing pooling criteria. Subgroups should be pre-specified, and strategies for managing heterogeneity across study designs must be outlined. In the implementation phase, data harmonization is essential. This includes, but is not limited to, standardizing adverse event and concomitant medication coding, aligning treatment-emergent periods and analysis visit windows, normalizing exposure durations, and unifying reporting units for laboratory or other common tests. Transparency in pooling algorithms and traceability to source datasets are vital for regulatory confidence. These considerations together support a robust ISS that informs safety conclusions across diverse development programs.

INTRODUCTION

Preparing an Integrated Summary of Safety (ISS) can feel daunting given the number of clinical studies involved. This paper aims to demystify the process by organizing it into two stages (design and implementation), highlighting key considerations and providing practical examples to illustrate recommended approaches.

ISS IN REGULATORY SUBMISSIONS

The ISS provides formal integrated analyses of safety data pooled across multiple clinical studies to inform the overall risk profile of a drug. The United States Food and Drug Administration (FDA) considers it a critical component of the clinical safety portion of a marketing or licensing application. Therefore, the ISS is required in applications submitted to the FDA in accordance with the regulations for new drug application (NDA) submissions (21 CFR 314.50(d)(5)(vi)(a)). Although there are no corresponding regulations requiring an ISS for biologics license application (BLA) submissions, applicants are encouraged to provide these analyses [1].

These submissions follow the Common Technical Document (CTD) format. CTD is a common format from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) for the organization of the quality, safety and efficacy data included for regulatory submissions, enabling efficient global review practices. The CTD is organized into five modules, Module 1 holds regional administrative information, Module 2 holds quality overall summary, non-clinical overview, non-clinical summary, clinical overview, and clinical summary. Module 3 details quality data, Module 4 details non-clinical study reports and Module 5 details clinical study reports. Module 1 s region-specific and Modules 2–5 are intended to be common for all regions, supporting a consistent submission backbone across health authorities [2].

FDA guidance places the ISS in Module 5.3.5.3 Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses), with cross-references to Module 2.7.4 (Summary of Clinical Safety) where appropriate [1]. FDA further clarifies that CTD "summary" sections in Module 2 are not the correct location for the full integrated analyses and that the ISS belongs in Module 5.3.5.3 except in rare cases.

For submissions to other agencies globally, including the European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom, Pharmaceuticals and Medical Devices Agency / Ministry of Health, Labour and Welfare (PMDA/MHLW) in Japan, and Health Canada, a standalone ISS is not uniquely specified in the same way as under U.S. NDA regulations. However, because these submissions are also required to follow the CTD/eCTD structure (limited to New Drug Submission [NDS], Abbreviated NDS [ANDS] and supplements [SNDS, SANDS] for Health Canada), which includes sections intended to support integrated safety evaluation, ISS-like integration work remains a practical requirement to support the safety summaries and integrated clinical conclusions within the document [2,3,4].

CONTENT FOR ISS

FDA describes the Integrated Summary of Safety (ISS) as a comprehensive, integrated evaluation of the drug's safety based on all available safety information; it is a detailed integrated analysis rather than a brief summary document. Consistent with the FDA guidance [5], an ISS should include a table of all investigations, the overall extent of exposure (e.g., number exposed by dose and duration), and the demographic and other characteristics of the pooled safety population. It should provide a structured evaluation of adverse experiences in clinical trials, including an overall narrative, displays of adverse events and occurrence rates using meaningful groupings (by study and by event), and analyses of adverse event rates; focused assessments of deaths, adverse-event–related

discontinuations, and other serious or potentially serious events are also expected. The ISS should further summarize and evaluate clinical laboratory data (and other safety assessments as applicable), incorporate adverse events and laboratory abnormalities from sources beyond clinical trials (including pertinent animal data and other relevant sources), and assess clinically meaningful drug–drug interactions and drug–demographic/drug–disease interactions using both formal PK/PD studies and clinical trial experience. For products intended for chronic use, FDA's outline also anticipates attention to long-term adverse effects and potential withdrawal effects, where relevant. Finally, FDA's guidance notes that periodic safety update reports for pending applications should contain the same kinds of information and follow the same integrated format, emphasizing that the ISS should be organized in a way that is reproducible and maintainable across the submission lifecycle.

ISS WORKFLOW

The credibility of ISS conclusions is determined largely by design-phase planning, including pre-specifying objectives, study selection and pooling criteria, analysis populations and time-at-risk definitions, and a strategy for handling heterogeneity across studies. At the same time, these design decisions must be executed consistently through harmonized derivations and traceable integrated datasets, so that outputs can be reproduced and defended during review. **Figure 1** summarizes this planning-to-implementation workflow and provides a roadmap for the sections that follow. The process begins with design-phase planning (objectives, study selection, pooling strategy, prespecifying conventions including treatment-emergent definitions, exposure adjustments, visit mapping and subgroup/heterogeneity strategy etc., and output specification) and transitions to execution-phase implementation (standardization, integrated derivations, QC/traceability, and final outputs), consistent with FDA's expectation that the ISS is a detailed integrated analysis typically located in CTD/eCTD Module 5.3.5.3. Integrated derivations in the ISS implementation phase follow the conventions specified during planning, so those points are discussed under the implementation section below. To focus our paper on methods and decisions, output specification and generation are left out of the discussion. Traceability is mentioned in related sections rather than a standalone topic.

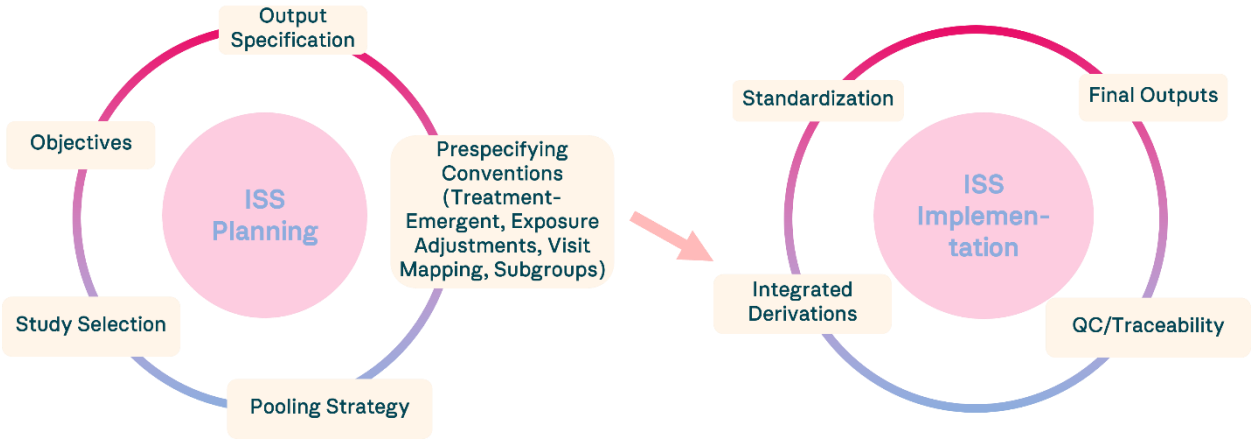

Figure 1. Planning-to-implementation workflow for ISS delivery

PLANNING FOR ISS

Although the ISS is assembled for a marketing application, its feasibility and interpretability are largely determined earlier, when protocols, data standards, and safety data capture can still be influenced. Program-level safety planning frameworks recommend initiating integrated safety planning early and refining it as evidence evolves (e.g., defining safety topics of interest and standardizing collection/definitions across studies) [6,7]. FDA/PHUSE webinar highlights that integrated planning documents are often produced too late, missing the opportunity to influence protocol approvals and targeted data collection for safety topics of interest [8]. FDA statistical perspectives further emphasize considering key safety design and data-collection elements prior to Phase 3, reinforcing why at End-of-Phase 2 before Phase 3 is a practical time for ISS-readiness planning [9]. Finally, FDA has described Type C meetings focused on ISS safety analysis strategy and related data requirements as a mechanism to align on pooling strategy, adverse events of special interest (AESI) approach, analytic methods, and data standards before extensive pooled programming begins, reinforcing that integrated safety strategy should be articulated early enough to obtain feedback and guide execution [10].

REGULATORY AND ANALYSIS OBJECTIVES

The first step in ISS planning is to define the regulatory decision context the ISS is intended to support, including the submission type, reviewing agency/region(s), indication, target population, and intended regimen. This context determines which safety evidence must be sufficiently robust (i.e., "decision grade") to inform benefit–risk evaluation and risk communication, because benefit–risk assessment is case specific and depends on therapeutic context, the

totality of evidence, uncertainty, and available risk management options [11]. In practical terms, the regulatory objective drives downstream ISS planning choices on (i) study scope (which studies are in-scope for the submission decision), (ii) pooling boundaries (which populations/regimens are comparable enough to combine for interpretable summaries), (iii) prioritized safety questions (e.g., key risks/AESIs and subgroups that are most relevant to the intended use), and (iv) the criteria for specific analyses (e.g., emphasizing controlled comparisons when available versus relying on well-characterized descriptive evidence when controls are limited) [8,11].
Within the regulatory decision context, there are four distinct ISS analysis objectives: signal detection, signal clarification, signal characterization, and signal communication [8,12]. Detection uses broad integrated summaries to find safety signals, which should be followed up by clarification to ensure the signal is true. Characterization is the deeper assessment of the true signals (e.g., time course, seriousness/severity, outcomes, exposure/duration patterns, and key subgroups). Finally, communication represents the curated subset of ISS analyses intended to support benefit–risk messaging and risk communication (including labeling-supportive summaries where applicable).

STUDY SELECTION

Study selection establishes the integrated safety evidence base (which trials can contribute to the ISS at all). This step is largely objective-driven because CTD expectations emphasize integrated safety conclusions for the intended patient population with transparent, reviewable summaries of exposure and safety outcomes [13]. All inclusion and exclusion decisions should be justified and clearly documented.
Two key considerations we would like to recommend for study selection are:

- **Indication / target population relevance.**
  Include studies relevant to the intended indication and target population; exclude studies with a materially different indication/population if pooling would compromise interpretability of the integrated safety conclusions for the intended population. FDA/PHUSE webinar also recommend to separate healthy volunteers from patients [8].
- **Data collection consistency.**
  Include only studies whose safety data collection and structure allow consistent integrated derivations (e.g., treatment emergent windows, mapping to common definitions) and traceability back to source. Where safety data collection is fundamentally incompatible, exclude from the integrated evidence base and present separately instead.

Here we use a mock example for illustration purposes. This sample clinical program has 7 clinical trials. The indications, clinical phase, population, design, dose group and durations are summarized in Table 1. The planned submission the ISS supports is for indication A with Middle dose as the target clinical dose. The package is planned to be submitted globally. Indications A and B are driven by different key regulators on the same signaling pathway, whereas indication C is materially different. So, for integration purposes, study 6 was excluded since the indication is not compatible with the target indication (fails rule 1), while studies in indications A and B are close enough to be pooled together. Study 7 was also excluded because the safety data collection in this investigator-sponsored study is incompatible with the rest of the studies (fails rule 2). Studies 1-5 constitute the integrated safety evidence base. As stated, the Middle Dose Group is the target clinical dose. The Low and High Dose Groups are simplified groups lumping all doses below or above target clinical dose together respectively. ‘x Weeks’ in the duration means the duration is not fixed.

Table 1. Sample Clinical Program Trial Summary

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 years)	Randomized Middle + Active Comparator → Both Arms Middle	52 Randomized Treatment + x Extension
A	Ph2	4	Child (1-<18 years)	Open Label Middle	52 Treatment + 52 Weeks Extension
B	Ph1	5	Adult	Open Label Low, Middle, High	4 Treatment + 44 Extension

Indication	Study Phase	#	Population	Design/Dose Group	Duration [weeks]
C	Ph1	6	Adult	Open Label Low, Middle, High	4 Treatment + 44 Extension
A	Investigator Sponsored	7	Child (1-<18 years)	Open Label Low, Middle, High	4 Treatment + x Weeks Extension

POOLING STRATEGY

After eligibility is established, pooling strategies must then be determined to assign eligible studies to pool/pools aligned with safety objectives and the evidence required to answer each objective. FDA/PHUSE guidance emphasizes prespecifying and documenting pooling strategies [8,10].

Below are some recommendations for pooling in integrated safety reporting:

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

Define multiple pools with clear intent: broad pools for signal detection, controlled pools for signal clarification, and subgroup and long-term pools for signal characterization. This structure supports transparent integration while avoiding misleading inference when clinical context differs [8,10,14].

- **Anchor core pools to the intended submission use-case.**

When there is a defined submission indication (A in our example) and a target clinical dose (Middle Dose in our example), the primary integrated safety communications should be anchored to Indication A at the Middle dose. This alignment ensures that integrated conclusions correspond to the intended population and regimen; other dose levels or indications can be informative but should be positioned as supportive rather than label-defining.

- **Separate controlled and uncontrolled evidence to protect interpretability.**

Randomized controlled periods provide the most informative anchor for clarification; open-label and extension periods expand exposure and support characterization but should not be mixed into comparative analyses in ways that dilute inferential strength [8].

- **Maintain traceability and consistent derivations across pools.**

Pooling strategy includes how derivations remain consistent (e.g., Treatment-emergent Adverse Event [TEAE] windows, period definitions, harmonized structures) and how traceability is documented for reviewer navigation. Traceability and consistent integrated derivations are determinants of successful integrated analyses and will ensure ease of interpretation. The details for this principle will be elaborated in the ISS implementation section below.

Applying the above principles to our sample clinical program, the pooling strategy for the ISS is proposed as below in Table 2. Dose-ranging information from Study 1 (Low/High vs Middle) was reviewed as supportive evidence for dose-response characterization for indication A, but it was not treated as a separate integrated pool since this is just one study.

Table 2. Safety Integration Strategy For Sample Program

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)

Pool ID	Pool name (short)	Primary objective(s) supported	Studies contributing	Dose focus	Period(s) included
P3	Controlled A + Middle Pool	Signal clarification (comparative anchor)	2–3 (randomized periods)	Middle dose compared with active control	Randomized controlled periods only

Pool P1 (All-Exposed Program Pool) is intended for broad signal detection and overall exposure context across Indications A and B. Because it intentionally maximizes sample size and patient-time, results from P1 are interpreted descriptively and can be stratified by indication (A versus B), population (adult versus child), dose group (Low/Middle/High where applicable), and study period (treatment versus extension) so that heterogeneity is transparent and subgroup signals are not masked.
Pool P2 (A + Middle Dose) supports the primary integrated safety information for the intended submission use-case: Indication A at the target clinical dose (Middle). This pool therefore excludes Indication B from primary conclusions and focuses on communicating the safety profile at the target regimen. Long-term safety at the target regimen can be characterized within P2 using exposure-duration stratified AE summaries (e.g., subjects with AE onset by cumulative duration categories and time-interval incidence), supported by exposure-adjusted incidence rates where appropriate. Pediatric versus adult subgroup analysis could be performed within this pool to support characterizing safety in specific (pediatric) population. While ICH E11 describes multiple pediatric age categories [15], this simplified mock example pools pediatric subjects into two bands, adolescent (12-<18 years old) and younger (<12 years old), to maintain interpretability and avoid sparse age strata.
Pool P3 (Controlled A + Middle) provides the main anchor for signal clarification because it retains a concurrent active comparator and is restricted to randomized treatment periods only. To preserve interpretability, post-randomization extension periods are not included in P3 comparative summaries and instead contribute to long-term characterization.
P3 can support signal communication (labeling) with comparative statements, while P2 can support descriptively.

IMPLEMENTING ISS

After the study selection and pooling strategy are established, the implementation phase operationalizes the design decisions through consistent derivations and integrated data structures so that outputs remain reproducible, traceable, and interpretable across studies despite differences in study design. The following discussion on implementation is not intended to be exhaustive; instead, we highlight only a few practical considerations that are most critical for preserving the integrity of the pooling strategy.

STANDARDIZING CODING

Standardizing medical coding across studies and over time is a foundational step for an ISS. Adverse events (and medical history, when included in the ISS) are typically coded using the Medical Dictionary for Regulatory Activities (MedDRA), while prior and concomitant medications are commonly coded using the World Health Organization Drug Dictionary (WHODrug) to support consistent aggregation and review across studies [16,17]. Because ISS programs often span multiple years, studies may have been coded using different dictionary versions. When coded terms are pooled across version boundaries, conceptually similar events can map to different Preferred Terms (PTs) or hierarchy placements, fragmenting counts across rows and potentially obscuring or diluting emerging patterns. A prespecified versioning strategy, including up-versioning and, when appropriate, re-coding to a consistent dictionary version for integrated analyses, helps ensure that similar events and similar medications are summarized together and that pooled outputs remain interpretable. In addition, MedDRA's granularity can make signal review challenging even when a single version is used. Therefore, ISS often supplements PT-level summaries with grouped-term analyses, such as Standardised MedDRA Queries (SMQs) and Customized MedDRA Queries (CMQs), to retrieve clinically coherent sets of terms aligned to topics of regulatory interest and to enhance sensitivity for signal detection and characterization. For transparency and traceability, the ISS should document the dictionary name and version used as well as the grouped term algorithm if used.

ALIGNING TREATMENT-EMERGENT PERIOD DEFINITION AND NORMALIZING TREATMENT DURATION

According to ICH E9 [18], treatment emergent (TE) is defined as "An event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state." For ISS, the practical meaning of "during treatment" must be prespecified as a time-at-risk window anchored to exposure (start at first dose within the relevant analysis period, and end at last dose plus a justified post-treatment window) [19]. This prevents inconsistent TEAE classification when pooling across heterogeneous study designs and provides a transparent basis for integrated summaries.
Where feasible, the ISS TE definition should align with each study's prespecified TE conventions; when studies differ (e.g., different post-treatment windows or rollover logistics), a harmonized program-level TE algorithm should be applied for integrated outputs and the mapping from study-specific rules to the ISS rule should be documented for traceability. This harmonization is particularly important at parent-to-extension study transitions when a dosing break

occurs: events with onset during the gap should be attributed according to the prespecified time-at-risk definition (e.g., counted as TE for the parent study period if onset falls within the parent post-treatment window; otherwise treated as off-treatment until extension dosing begins). Dose changes also require explicit attribution rules. In the mock program, comparative signal clarification (P3) should restrict TEAEs to randomized controlled periods, while descriptive characterization at the target regimen (P2) can incorporate extension exposure.

Because TE classification is defined on a prespecified time-at-risk window anchored to exposure, exposure-duration normalization for integrated safety summaries is realized primarily through exposure-adjusted incidence rates (EAIR), defined as “The number of patients with an event divided by the total time at risk for the event”, since it uses patient-time denominators when treatment duration or follow-up differs meaningfully across studies or periods. Where clinically relevant (e.g., recurrent events where event burden matters), exposure-adjusted event rates (EAER) may be reported as a complementary measure, which is defined as “The number of events (if a patient has more than one occurrence of the same event, all occurrences are counted) divided by the total time exposed” [20].

ALIGNING VISIT WINDOWS

Aligning visit windows is a high-impact step in ISS implementation because contributing studies often differ in planned visit schedules, target days, and follow-up structure, and subjects may complete visits outside nominal windows or have multiple assessments near a target timepoint. When pooled without a consistent approach, longitudinal safety summaries (e.g., laboratory tests, electrocardiograms [ECG], and vital signs) can fragment across heterogeneous nominal visit labels and reduce temporal comparability. Assigning records to analysis visits using unified prespecified rules that map observed assessments to intended timepoints can improve data comparability and interpretability.

To make the implementation discussion concrete, the mock sample program assumes a common pattern in which early safety assessments are more frequent and later follow-up is less frequent. All studies are assumed to include early visits at Day 8, Week 4, and Week 8. After Week 8, some studies have scheduled visits at Week 13/26/39/52 etc at every 13 weeks (Q13W) cadence whereas other studies have scheduled visits at Week 26/52 etc. at every 26 weeks (Q26W) cadence. Studies 1 and 5 have a total duration of 48-weeks thus use Week 12/24/36/48 instead of Week 13/26/39/52. These differences reflect common protocol variability across a multi-study program and motivate the need for an explicit ISS visit-alignment strategy.

Given the mock program scenario, the ISS first defines a common analysis-visit spine that preserves early time-course interpretation while remaining compatible with both Q13W and Q26W schedules: Day 8, Week 4, Week 8, a Quarter-1 milestone (Week 12/13), a mid-year milestone (Week 24/26), and one-year milestone (Week 48 for Study 1 and Study 5 and Week 52 for other studies) and Q26W after that. When it comes to how to map individual visits to the ISS analysis visits, there are two acceptable methods described below:

Method 1: ISS-level windowing (direct derivation of ISS analysis visits). Under this approach, the ISS assigns each record to the ISS analysis-visit spine using date-based windows anchored to a common reference (e.g., first dose or period-specific first dose, depending on the analysis purpose). This method is conceptually identical to individual-study visit windowing (analysis visits versus raw visit labels) but applied consistently across pooled studies so that the same ISS timepoint represents comparable timing across studies. For traceability, ADaM conventions support capturing these assignments using AVISIT/AVISITN (or ATPT/ATPTN) and analysis windowing variables (e.g., window boundaries and distance-to-target) to document how records were mapped to timepoints.

Method 2: Study-native AVISIT mapping (reuse individual-study analysis visits). This approach is preferred when the goal is to remain closely aligned with individual study output. It leverages study-native analysis visits already defined in each study’s ADaM (AVISIT/AVISITN), and then map those study analysis visits to the ISS spine. For the mock program, examples of mapping include: Study 1 and Study 5 Week 12 to the ISS Week 12/13 milestone; Q13W studies’ Week 13 to the same milestone; Week 24 or Week 26 to the ISS Week 24/26 milestone; and Week 48 or Week 52 to ISS one-year milestone. This approach preserves each study’s prespecified windowing and record-selection logic when it exists, thereby maintaining close alignment with study-level results while still enabling pooled reporting at harmonized ISS timepoints. This method works best when the study-native AVISIT represents an analysis construct. If some studies in the program did not perform windowing and instead carried nominal visit labels forward into analysis, those visits can reflect off-schedule timing or site-level labeling inconsistencies thus reduce comparability when mapped into a common ISS spine. In such cases, the ISS can apply a lightweight ISS-level date-based mapping for that study only. To preserve traceability, the ISS should keep individual study VISIT/VISITNUM and any AVISIT/AVISITN (if present) and add integrated variables documenting the harmonized ISS analysis visit assignment.

The same alignment framework can be applied to longitudinal safety domains such as laboratory tests, ECG, and vital signs; however, the appropriate record-selection conventions may differ by domain (e.g., multiple observations within a window for labs; replicate readings for ECG; and sensitivity to measurement positions for vital signs).

TEST VALUE COMPARABILITY

For integrated safety summaries, continuous measures (laboratory tests, ECG parameters, and vital signs) are only comparable across studies when three elements are standardized: (1) measurement units, (2) interpretation relative to reference ranges (especially when data come from mixed central and local laboratories), and (3) potentially clinically significant (PCS) criteria used to flag clinically meaningful abnormalities.

Unit unification should be approached with traceability and reviewer interpretability in mind. At minimum, the ISS should preserve both the original values/units and a standardized representation used for pooled analyses. FDA has described an agency-wide effort toward broader acceptance of laboratory data reported in SI units while acknowledging that many U.S. reviewers and clinicians are most familiar with U.S. conventional units; in the absence

of a full transition in the U.S., FDA notes that conversion of certain lab results to conventional units may be a necessary interim step for interpretability. FDA therefore strongly encourages sponsors to solicit input from review divisions as early as possible, ideally before Phase 3 and potentially at End-of-Phase 2, to minimize the risk of late conversion requests during NDA/BLA review. [21]

Reference range harmonization is particularly important when central and local laboratories both contribute. Rather than pooling solely on raw H/L/Normal flags, integrated analyses could interpret results using the fold of the recorded lower/upper limits of normal (LLN/ULN) associated with each measurement (or a documented normalization approach relative to individual record limits), so that pooled summaries reflect clinically meaningful deviations [22].

PCS criteria should be prespecified (or transparently mapped from study SAPs) so pooled counts represent consistent clinical meaning across studies. Examples of program-level PCS screens include Hy's Law-type liver test patterns (e.g., ALT/AST and total bilirubin assessed relative to ULN) for hepatic signal detection, which aligns with FDA guidance on premarketing Drug Induced Liver Injury evaluation and Hy's Law concepts [23]. For ECG, PCS criteria are commonly defined using protocol- and program-level QT/QTc outlier thresholds and change-from-baseline concepts, consistent with the ICH E14 framework emphasizing ECG methodology and safety monitoring considerations [24]. For vital signs, PCS criteria can be based on clinically established definitions such as orthostatic hypotension, which relies on blood pressure changes after posture change within a specified time window [25].

CONCLUSION

In this paper, we framed successful ISS development as a two-stage process: planning and implementation. We used a mock sample program to illustrate how key design choices translate into practical execution. Overall, the paper is intended to provide a clear thought process for ISS planning and to highlight a key set of implementation decisions that strongly influence interpretability, traceability, and reviewability. Together, these practices strengthen the ISS, enhance confidence in the safety evidence supporting the marketing applications, and facilitate efficient regulatory review and decision making.

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