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ISS between FDA, EMA & NMPA: Similarities vs. Differences & Programming Tips

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ABSTRACT:

Integrated Summary of Safety (ISS) is the requirement part by the regulatory members of the International Conference on Harmonization (ICH) for investigational new drug application (IND). ISS shows the overall safety profiles for certain investigational drugs, including reports of all clinical studies of safety. According to ICH. M4, FDA, EMA, and NMPA raised their guidance for the pharmaceutical industry, which detailed and clarified the requirements and elements for ISS.

In this paper, the similarities and differences from the programming's perspective will be summarized for these FDA, EMA, and NMPA guidance of ISS sections, including differences between 2.7.4 & 5.3.5.3, and general contents for ISS as well as the differences for FDA, EMA & NMPA submissions. Moreover, the corresponding programming points like procedures and tips when pooling for multiple studies on safety domains will also be discussed.

INTRODUCTION:

ICH has the M4 series of guidance, for the ISS part especially in "ICH. M4(R4): Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use. 2016" and "ICH. M4E(R2): Common Technical Document for the Registration of Pharmaceuticals for Human Use – Safety. 2002". These ICH.M4 Chinese version documents were also published in 2016.

Both FDA, EMA, and NMPA have raised guidelines for an investigational new drug application (IND). FDA has "Guidance for Industry on Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document. 2009" to clarify the location for ISS and ISE and "Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies Guidance for Industry (DRAFT GUIDANCE).2021" to clarify procedures and requirements for IND. EMA also published the ICH guideline and QA part for ISS on the website.NMPA has 《新药临床安全性评价技术指导原则（征求意见稿）, 2022》 to introduce the detailed contents.

This paper will introduce two parts about ISS. One is the similarities and differences in programming's perspective for FDA, EMA, and NMPA guidance. We will first clarify ICH 2.7.4 vs 5.3.5.3, then introduce the general contents as well as the differences for FDA, EMA & NMPA submissions from the programming's perspective. The other part is presenting our experience for integration and sharing some tips.

SIMILARITIES VS. DIFFERENCES FOR FDA, EMA, AND NMPA GUIDANCE

ICH Section 2.7.4 vs 5.3.5.3

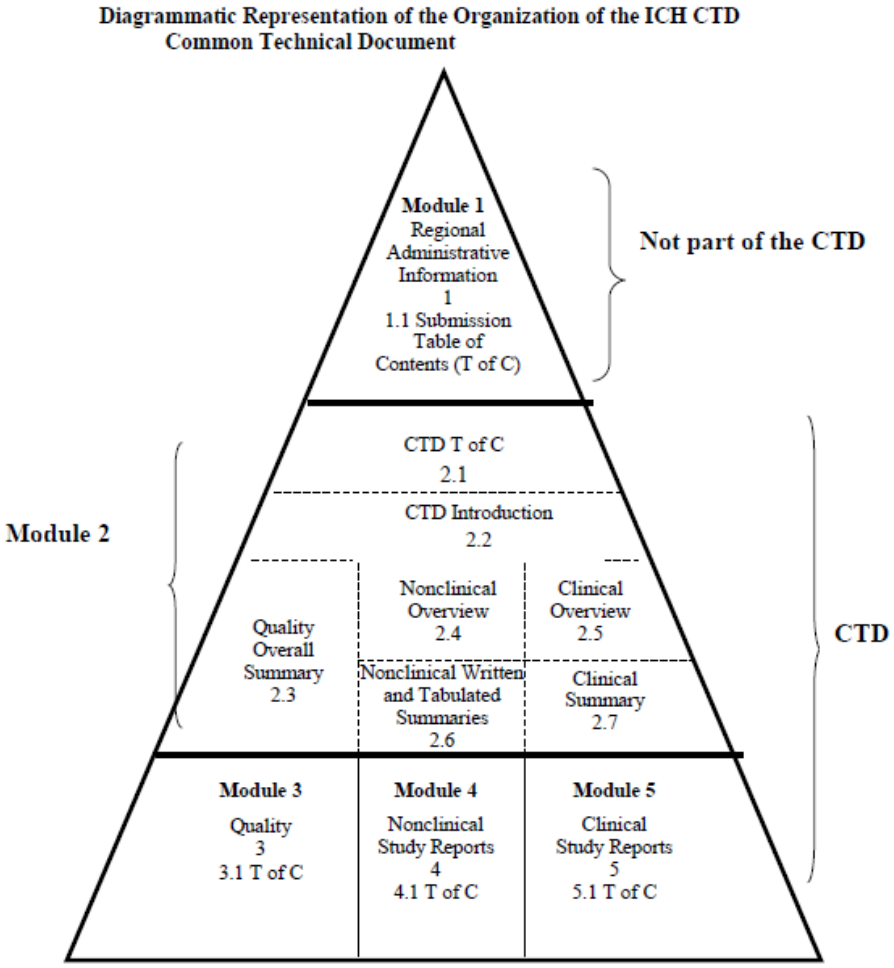

Table 1

Section 2.7.4 is Summary of Clinical Safety and Section 5.3.5.3 is Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses). We need to clarify that the Common Technical Document (CTD) summary sections in Module 2 are not the correct location for ISS, but Module 5 – Section 5.3.5.3 should be the location for ISS.

The Clinical Summary (Section 2.7) provides a detailed and factual summarization of all clinical information in ICH E3 clinical study reports. The length of Section 2.7 will be in the range of 50 to 400 pages. The Clinical Study Reports (Module 5) includes information on any meta-analyses or other cross-study analyses for full reports and postmarking data. Section 5.3.5.3 contains clinical reports with a detailed description and presentation of the extensive clinical analyses.

In FDA guidance "Guidance for Industry on Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document. 2009": Module 2 is the appropriate location for Efficacy and Safety Overview and Summaries; Module 5 is the appropriate Location of the ISE and ISS with no space limitation. These scenarios are acceptable: 1) full ISS is placed in 5.3.5.3 and the text portion of the ISS is summarized in 2.7.4 if large ISS, or 2) full ISS is placed in 5.3.5.3 and the text portion of the ISS is repeated in 2.7.4 if small ISS, or 3) small ISS: text portion in 2.7.4 and the appendices and datasets are placed in 5.3.5.3.

FDA has also illustrated ISS summary or full ISS in U.S. Regulation of 21 CRF 314.50(c)(2)(viii) and (d)(5)(vi), indicates that 2.7.4 is the summary of the clinical data section of the NDA and 5.3.5.3 is the clinical data section, which describes the clinical investigations of the drug.

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

Table 2: ISE- and ISS-related SECTIONS WITH CORRESPONDING Regulations

General Contents for ISS & Differences for FDA/EMA/NMPA

According to ICH M4E (R2), 2.7.4 Summary of Clinical Safety includes these contents:

2.7.4.1 Exposure to the Drug

2.7.4.2 Adverse Events

2.7.4.3 Clinical Laboratory Evaluations

2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

2.7.4.5 Safety in Special Groups and Situations

2.7.4.6 Postmarketing Data

2.7.4.7 Appendix

The contents in ICH M4 series guidance are the same among FDA, EMA, and NMPA, with language or grammar slightly different.

FDA with U.S. Regulation of 21 CRF 314.50 (d)(5)(vi) describes ISS in the clinical data section. ISS is the integrated summary and updates of safety information including all available safety information of study drugs about pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations,

such as data from epidemiological studies of related drugs. The safety data must be presented by gender, age, racial subgroups, and other subgroups when appropriate. Also, this may be updated periodically if new safety information may affect the draft labeling.

NMPA released 《抗肿瘤创新药上市申请安全性总结资料准备技术指导原则》 on Dec 2022, which aim at guiding anti-tumor drugs' application, including the displaying logic, the recommended grading and dosing, exposure, safety profile, AESI, SAE & death, and other safety materials. This guidance is much recommended for reference in my view. Also has published 《新药临床安全性评价技术指导原则》（征求意见稿）on Oct 2022. In this guidance's Section 6: 新药上市申请时的安全性评价, there is the detailed instruction for safety reporting for IND, including the overall extent of exposure and safety data analysis.

From the programming's perspective, we need to generate ADaM datasets like ADSL, ADEX, ADAE, ADLB, ADVS, ADPE, ADEG, ADCM, ADPR, and ADMH (and others if needed) for ISS. In each dataset, we need to refer to the guideline for the analysis scope.

ADSL: 1) Analysis population. 2) Treatment group. 3) EOT, EOS Reasons' Standardization. 4) Exposure information (Treatment Duration, Cumulative Dose (Mean, Median), Dose Intensity, Relative Dose Intensity, Dose Reduction, Dose Interruption, Dose Withdrawn)

ADAE: 1) standardize the MedDRA version among all integrated studies. 2) Confirm the adverse drug reaction (ADR) with Physicians. 3) Confirm the adverse events of special interest (AESI) categories. 4) Treatment-Emergent AE (TEAE), Treatment Related TEAE (TRAE), SAE, life-threatening AE, Death. 5) AE with Exposure: AE leads to dose interruption/reduction/withdrawal.

ADLB: CTCAE Grade; abnormal hepatic laboratory values (Hy's Law criteria). Note to use the unique rule among different studies.

ADPE, ADVS, ADEG: Physical/Vital Signs/ECG Tests.

PROGRAMMING PROCEDURES AND TIPS

Analysis Scope

For the ISS programming procedures, we need to first clear the analysis scope, like 1) which studies as well as the basic information like study status, enrolled subjects, etc, should be included in this ISS analysis; 2) which population set and treatment group should be displayed among the multiple clinical studies. This information will be described in the integrated statistical analysis plan (SAP). According to the SAP & mockups, programmers can start the coding work for the integrated datasets and Tables, Listings, and Figures (TLFs); 3) In this analysis, which part of safety analysis is needed or not? Like demographic characters and any subgroup (e.g. race groups, age groups) analysis; adverse event, treatment-emergent adverse event; any treatment-emergent special interest adverse event; any treatment-emergent adverse drug reaction (ADR); any abnormal values and clinically significant assessment of laboratory evaluations, vital signs, physical findings, and other observations related to safety.

Pre-requisite

There are some general procedures and points we need to clear. Firstly, we need to choose the suitable source data for each study for the pooling, like raw data to ADaM, SDTM to ADaM, or ADaM to ADaM following CDSIC standards. Moreover, the formats of datasets also need to be converted, like keeping common variables, the length and the label of these variables should also be adjusted.

Data-cut-off for Ongoing Studies

For ongoing studies, we also need to apply the data-cut-off rule for date and time variables in the pooling datasets when integrating, like ADSL.RFICDT: If the informed consent date is later than the cutoff date, the patient will be not included in any domain.
ADAE/ADCM/ADPR.ASTDT/AENDT: if the start date is later than the cutoff date, the record will be removed; if the start date is earlier than the cutoff date and the end date is later than the cutoff date, then the end date will be set to missing and the outcome will be set to recovering/resolving; collection/test dates in ADLB/ADEG/ADVS: If the collection/test date is later than the cutoff date, the record will be removed.

Treatment Map/Baseline Re-assign

Different studies may have different designs like one treatment/period in paralleled studies while cross-over studies may have multiples (like a double-blind period & open-label period). The data sets' structures for these studies will be different as well. In this condition, treatment group variables like ARM/ACTARM/TRTxxG/TRTxxA and baseline variables like ABLFL and some analysis flags need to be standardized.

Translations for FDA/EMA vs. NMPA IND

In some conditions with multiple study sites or multiple studies among different countries, the languages for studies may be different: like English and Chinese. The translation is required for submission in different countries, like FDA/EMA or NMPA. There are some points that need to be discussed with the study team and get suitable results. For example, how to translate and unified the End of Treatment (EOT) and End of Study (EOS) reason, text-free information like collected adverse event terms and concomitant medication drugs. We also need to translate the MedDRA and WHODrug dictionary variables for different languages. Although we can refer to the Controlled Terminology for reference on unifying some variables, the text-free information should be considered.

Unify and Recoded the Coding Dictionaries

Then we need to update the coding dictionaries to keep all the studies consistent versions, including Medical Dictionary for Regulatory Activities (MedDRA) and WHODrug. As these integrated studies may start over many years, the coding dictionaries will not be the same version. For ADAE, dictionary variables like dictionary-derived term (AEDECOD) and body system or organ class (AEBODSYS), should be updated coding version via the lowest term code. For ADCM, the standardized medication name (CMDECOD) and the ATC level text variables should also be updated to the unique coding version.

Programming Tips in our experience

Create the Integrated Dataset

After aligning the analysis scopes and all prerequisites as this paper talked about in the previous part, we can start integrating datasets. There are several approaches for preparing integrated ADaM data, three approaches are discussed here: raw data to ADaM, SDTM to ADaM, and ADaM to ADaM following CDSIC standards.

The best case is to use the study-level ADaM datasets to generate the integrated ADaM datasets. Often, the study is completed or almost complete with the main programming work, so the study-level ADaM datasets are ready to use. We should adjust the inconsistencies in each ADaM dataset, keep the required variables in the data and align the unique deviation rule; use the same structure template; so that we can use the integrated ADaM datasets for TLFs directly.

Other common cases are to use the study-level SDTM or CDASH raw datasets to generate the integrated ADaM datasets. In these circumstances, the study is/studies are still ongoing, or is the legacy study, and not very mature to use the ADaM datasets when pooling. In my experience, the toughest work is generating the study-level integrated ADSL with study-level SDTM or raw data. We should consider the cut-off rule and all the deviation rules within each study ahead of pooling.

Standardize Tests in Clinical Laboratory Evaluations, Vital Signs, Physical Findings, and Other Observations Related to Safety

ADLB, ADVS, and ADEG should use the standard files within the integrated studies.

ADLB: Unified results and standard units, CTCAE version, integrate lab tests in CTCAE shift tables, hy's law criteria, and the analysis flags.

ADVS, ADEG: integrate the Tests, Unified results, and standard units for Vital Signs and ECG tests among multiple studies, the analysis flags.

Have these standard files with raw parameters, raw unit, standard unit, standard results, conversion factors, and standard parameters, included in the analysis parameters (defined in SAP). Use the standard file to gain the required tests first and then derive the required results variables and analysis flag variables.

CONCLUSION

ISS is the requirement when IND. Both FDA, EMA, and NMPA raised ICH M4 guidance and introduced ISS detailed for the contents and procedures. Section 2.7.4 is the summary of clinical safety while the full clinical safety report should be located in section 5.3.5.3. There is no big difference among the three regions for ISS. But NMPA raised "抗肿瘤创新药上市申请安全性总结资料准备技术指导原则" for anti-tumor drugs when IND. In this guideline, the general analysis structures are described. We need to know the analysis scope and standard rules for programming before coding. This paper also provides some programming scope and tips in the general contents. These tips can be references and help improve the efficiency when pooling the ISS datasets.

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