Understanding the Differences and Effectively Transitioning Between the US Integrated Summaries of Effectiveness and Safety (ISE/ISS) and the CTD Summaries of Clinical Efficacy and Safety (SCE/SCS)

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The adoption in 2000 of the Common Technical Document (CTD) format for marketing applications notwithstanding, the US regulations requiring an integrated summary of effectiveness (ISE) and an integrated summary of safety (ISS) remain in effect. Many applicants, however, have attempted to use the CTD module 2 clinical summaries, specifically the summary of clinical efficacy (SCE) and the summary of clinical safety (SCS), alone to fulfill the regulatory requirements for an ISE and ISS, arguing that it is redundant to submit a separate ISE and ISS in addition to the SCE and SCS. Consequently, the US FDA has issued numerous guidances and made podium presentations communicating the message that, except in rare circumstances, New Drug Applications should contain the ISE and ISS documents as well as the CTD summaries of clinical efficacy and safety (SCE and SCS). The core difference between the ISE/ISS and their corresponding clinical summaries is in the depth of the analyses and the amount of information needed to support the analyses. While documenting the larger integrated analyses of efficacy and safety in the ISE and ISS, applicants should develop a strategy and process for deriving the SCE and SCS. Ultimately, submitting detailed and fully comprehensive ISE and ISS documents not only enables applicants to comply with regulations, but may also facilitate quick and efficient preparation of the SCE and the SCS.

Key Words
Integrated summary of effectiveness; Integrated summary of safety; Summary of clinical efficacy; Summary of clinical safety; Common Technical Document

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INTRODUCTION

Since the introduction of the Common Technical Document (CTD) in 2000, the US FDA has observed an increase in the number of New Drug Applications (NDAs) that do not contain sufficiently detailed and fully comprehensive integrated analyses of efficacy and safety. It appears that this trend is due to an attempt by some applicants to use module 2, section 2.7.3 of the CTD, the summary of clinical efficacy (SCE) and module 2, section 2.7.4 of the CTD, the summary of clinical safety (SCS) alone to fulfill the US regulatory requirements for an integrated summary of effectiveness (ISE) and an integrated summary of safety (ISS). To justify their actions, these applicants have argued that it is redundant to submit a separate ISE as well as an SCE and a separate ISS as well as an SCS. In reaction to this trend, FDA has on numerous occasions clarified the differences and similarities between the ISE/SCE and the ISS/SCS.

Our objective in this article is to demonstrate that, rather than being a redundant exercise, the preparation of an ISE and an ISS that fully document the comprehensive integrated analyses of efficacy and safety, respectively, remains the preferred way to satisfy the US regulatory requirements. Furthermore, proper development of the ISE and ISS, which capitalizes on the harmonized format and structure of the CTD, may well facilitate quick and efficient preparation of the SCE and SCS. Following this approach can help expedite review of the application and can also be expected to minimize the risk of receiving a "refuse to file" letter. Although the US regulations for a Biologics License Application (BLA) do not necessitate including an ISE or ISS per se, the concepts described herein for NDAs can and should be

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generally applied to BLAs, as stated in the introduction to the draft "Guidance for Industry: Integrated Summary of Effectiveness" (hereafter referred to as the ISE Guidance) "applicants are encouraged to provide these analyses in their [biologic license] applications" (1).

HISTORICAL BACKGROUND

In 1985 the US Food and Drug Administration implemented a major overhaul to the NDA regulation (21 CFR 314.50) (2) in what is commonly referred to as the "NDA rewrite." Among other things, the NDA rewrite called for the following comprehensive efficacy and safety analyses, which remain a requirement to this day:

- ISE, 21 CFR 314.50(d)(5)(v): An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications.
- ISS, 21 CFR 314.50(d)(5)(vi): An integrated summary of all available information about the safety of the drug product, including 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.

In 2000, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) recommended that the CTD be adopted to establish a common format and organization for regulatory dossiers across regions and regulatory authorities. One of the CTD guidance documents, ICH M4E (3), describes the organization of clinical information in a marketing application, including, but not limited to, the clinical summary (module 2, section 2.7), which is a multicomponent document that addresses clinical data summarization and integration. In particular, sections 2.7.3 and 2.7.4 of ICH M4E provide guidance for the SCE and the SCS, respectively. As stated on the ICH website (4), the ICH guidelines are implemented by each regulatory cosponsor according to its national or regional regulations, and are intended to be used in combination with regional requirements. Thus, the introduction of the CTD format did not change or supersede the US regulatory requirement to include both an ISE and an ISS in an NDA.

SIMILARITIES AND DIFFERENCES BETWEEN THE ISE/SCE AND ISS/SCS

The CTD was intended to create a more standard format and organization for regulatory dossiers by incorporating key aspects of regional submission documents, and in large part, this goal has been achieved. Key regulators from the United States, as well as from Japan and the European Union, comprised the steering committee that guided the creation of the CTD. Therefore, it is not surprising that the format and organization of the CTD clinical summaries (in particular the SCE and SCS) as specified in ICH M4E is based in large part on the format and organization of the ISE and ISS (as described in FDA's 1988 "Clin-Stat Guidance") (5). As noted in the "Guidance for Industry—Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document" (the Location Guidance), "the Module 2 clinical summary sections follow the outline of the ISE and ISS described in ICH M4E" (6). Further, one of the most important concepts regarding the relationship between the ISE and the SCE is that these documents describe essentially the same analyses of efficacy. Likewise, the ISS and the SCS each describe essentially the same analyses of safety.

In part, these similarities have led to the present confusion (or perhaps in some cases resistance) regarding the need to submit a separate ISE/ISS in addition to the SCE/SCS, as it may appear that preparing two sets of documents describing many if not all of the same analyses might be redundant. This confusion is compounded by the titles of the documents; the integrated summary of effectiveness (ISE) and integrated summary of safety (ISS) would appear from their titles to be summaries of the efficacy and safety analyses, as would the SCE and SCS. However, as has been stated multiple times now by FDA reviewers (7–9), the ISE and ISS documents are misnamed; they are, in fact, not summaries but integrated analyses. The core differ-

TABLE 1

ISE- and ISS-Related Sections With Corresponding Regulations

CTD Section	US Regulation	Comment
2.5 Clinical Overview (~30 pages) 2.5.4 Overview of Efficacy 2.5.5 Overview of Safety	N/A	Not a US 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)	US 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

ence between the ISE/ISS and their corresponding clinical summaries is in the depth of the analyses and the amount of information needed to support the analyses. Specifically, the SCE and SCS are typically summaries derived from the full exposition of the integrated analyses of efficacy (ISE) and safety (ISS). Therefore, text, tables, and figures that appear in the SCE or SCS may also appear in the ISE or ISS. However, the typical ISE or ISS will contain additional analyses and supporting documentation that are far more extensive than those summarized in the SCE or SCS. To formally communicate this message, in February 2004 FDA issued the "Guidance for Industry M4: The CTD—Efficacy Questions and Answers" (10). Q&A 10 of this document officially stated, "The ISS/ISE are critical components of the safety and effectiveness submission and are expected to be submitted in the application in accordance with the regulation. . . . Note that, despite the name, these are integrated analyses of all relevant data, not summaries." Continuing, Q&A 10 indicates that although the "sections of the CTD follow approximately the outline of the sections of the ISS/ISE . . . the CTD Clinical Overview and Summary in module 2 will not usually contain the level of detail expected for an ISS."

In fact, the ISE/ISS and the SCE/SCS meet separate and distinct requirements pertaining to US drug submissions. Table 1, taken from the Location Guidance, provides an excellent summary of how the ISE/ISS and SCE/SCS fulfill pertinent US regulations. Note that the SCE (referred to as 2.7.3 in Table 1) and the SCS (2.7.4 in Table 1) correspond to the US requirement for a clinical summary (21 CFR 314.50(c)(2)(viii)). Separately, the US requirements described in 21 CFR 314.50(d)(5)(v and vi) are fulfilled by the documents contained in module 5, section 5.3.5.3 (ie, the ISE and ISS).

The differences in the level of detail and amount of supporting documentation required for the SCE/SCS versus the ISE/ISS are further explained in other guidance documents. Specifically, the ICH M4E guidance indicates that the SCS (and the SCE by inference) should be a summary of the full integrated analyses of safety (and efficacy) that are routinely submitted in some regions (ie, the ISS and ISE in the US). Further, M4E recommends a page limit of 50 to 400 pages for the entire CTD clinical summary (ie, module 2, 2.7) and the Location Guidance suggests that large sections of supporting tables, appendixes, or data sets should not be included in the summary but placed in the larger ISS in module 5, section 5.3.5.3 (see below). Importantly, applicants are reminded that the SCE and the SCS are only two out of six subsections in the entire clinical summary. Therefore, applicants should be mindful of the size of the SCE and the SCS so that all sections of the clinical summary can be incorporated within the 400-page limit. Given that the integrated anal-

yses of efficacy and safety typically contained in the ISE or ISS can each consist of 1,000 pages of text, additional appendixes, and large data sets, these documents will certainly not fit within the page limits put forth by ICH M4E for the entire CTD clinical summary.

Anticipating that the detailed analyses and supporting documentation required by some regulatory authorities would be too extensive to fit within the page limits for the clinical summary, the ICH M4E also provided a separate location within the CTD for these additional details. According to the M4E guidance, when analyses are too detailed or extensive for inclusion in the clinical summaries, they should be presented in a separate report located in module 5, section 5.3.5.3 of the CTD structure labeled "Reports of Analyses of Data From More Than One Study (Including Any Formal Integrated Analyses, Meta-analyses, and Bridging Analyses)." For a US NDA/BLA, this concept described by ICH M4E is synonymous with preparing an ISE and an ISS and placing them in module 5, section 5.3.5.3.

However, in Q&A 10, FDA offered an exception by noting that the clinical summary "may contain the level of detail needed for an ISE, but this would need to be determined on a case-by-case basis." FDA further stated, "if the requirements of 21 CFR 314.50 can be met for a particular application by what is in the CTD Module 2 summary, then the CTD Module 2 section would fulfill the need for an ISS/ISE." These exceptions were reiterated in multiple presentations and formally documented again in the Location Guidance. Similar to the Q&A document, the Location Guidance states, "Generally, the Module 2 clinical summary sections (e.g., the SCE and SCS) follow the outline of the ISE and ISS described in ICH M4E; however, they do not describe the needed level of detail for an ISE or an ISS." However, the exceptions are noted as follows: "Only in unusual cases should the narrative parts of the full ISE or ISS and the summaries in sections 2.7.3 and 2.7.4 be the same." The Location Guidance also includes various graphical depictions of this concept.

As applicants have attempted to streamline their global regulatory submission efforts (particularly in light of the fact that many regions outside the US do not require an ISE or an ISS), they have increasingly keyed in on the exceptions noted above in an effort to prepare a single set of global regulatory documents. Thus, since the inception of ICH M4E, many applicants have argued that their US NDA submissions have included the ISE and ISS by way of the SCE and the SCS. Although FDA accepted many of these applications in the spirit of harmonization, the agency subsequently recognized that the SCE and SCS often lacked sufficient detail regarding integrated efficacy and safety analyses so that a thorough and timely review was impeded by the need to request more information from the applicant. Reviews by FDA have also been impeded in cases where applicants included too much information in the SCE and SCS so that these documents were no longer true summaries. In addition, there has also been a monumental increase in the level of governmental and public scrutiny directed at FDA regarding its approach to regulatory decision making for determining the effectiveness and safety of drugs. Thus, the agency's experience with submissions in CTD format coupled with the rising tide of scrutiny has led FDA to reinforce the message that applicants need to thoroughly assess the benefits and risks of their drug in a truly integrated fashion and document these analyses in the ISE and ISS while summarizing them in the SCE and SCS.

For efficacy, FDA's current thinking was put forth in the ISE Guidance, which states that "the ISE primarily is an integrated analysis of these data, going beyond a simple summary. . . . The document in section 2.7.3 should summarize these analyses, but, in most cases, the ISE will be substantially larger than what would be appropriate for the section 2.7.3 summary of these data and analyses." By analogy, it can be inferred that current FDA thinking regarding safety is similar; the document in section 2.7.4 should summarize the safety analyses, yet in most cases, the ISS will be substantially larger. Thus, the agency has reinforced its view that to fulfill regulatory requirements, NDAs should

generally include a full ISE (and a full ISS) in addition to a clinical summary. Alternative approaches will be considered the exception rather than the rule and will merit case-by-case discussion with the review division. A pre-NDA meeting would be an ideal forum for such a discussion. Accordingly, applicants who anticipate that the SCE and SCS may fulfill the US requirement for an ISE and ISS are encouraged to utilize the pre-NDA meeting to proactively provide a rationale and gain agreement on their alternative approach.

While some applicants seem to feel that FDA's position is contrary to the intent of the ICH, it is actually in keeping with ICH's goal of creating a common format and organization of regulatory dossiers to be used in combination with regional requirements. FDA has worked hard as part of ICH to ensure that the structure of the CTD encompasses a framework that enables applicants to efficiently prepare and submit NDAs that meet US regional requirements. Consequently, the similarities in structure and format of the ISE/SCE and ISS/SCS are no coincidence. By properly preparing an ISE and an ISS that meet US regulatory requirements, applicants will have also created a set of documents that may be readily condensed, mapped, and encapsulated to produce the SCE and SCS documents that meet the US requirement for a clinical summary. This approach can be expected to expedite the creation of high-quality, internally consistent documents, as well as to facilitate FDA's review.

DERIVING THE SCE AND SCS DOCUMENTS

Given the significant breadth and depth of efficacy and safety data contained in a typical NDA, the ISE and ISS will almost always exceed the capacity of the SCE and SCS documents; therefore, applicants will need to develop a strategy to derive the SCE and SCS from the larger integrated analyses. For example, the ISE will often explore similarities and differences among an extensive set of baseline characteristics to determine whether these factors influenced outcomes. To establish the robustness of the efficacy results and further substantiate the drug's benefits, the ISE may also delve into multiple efficacy analyses of primary, secondary, and tertiary endpoints (where appropriate) as well as more extensive analyses by study groupings, analysis populations, timing, and other factors. In addition, an ISE may often include confirmatory evidence of effectiveness from phase 2 trials. All of these in-depth analyses need to be described, often with text supported by in-text tables, figures, and listings (TFLs), end-of-text TFLs, data sets and numerous standard and ad hoc appendixes to produce a complete ISE that satisfies US regulatory requirements. Similarly, the ISS will contain highly detailed analyses of safety to identify critical safety signals that may be buried in the overall safety database. To find these needles in a haystack, applicants will need to analyze deaths, nonfatal serious adverse events, other significant adverse events, and common adverse events by a variety of factors to tease out important associations. Additional analyses by extent of exposure, organ systems, special syndromes, clinical laboratory values, vital signs, and numerous subgroups should also be documented in the ISS. Therefore, similar to the ISE, a complete ISS will include substantial amounts of text, in-text TFLs, end-of-text TFLs, data sets, narratives, and appendixes to adequately document the safety analyses and satisfy the US regulatory requirements.

Once the integrated analyses of efficacy and safety have been performed and fully documented in the ISE and ISS, the applicant's next task is to use those reports to derive the SCE and the SCS. These summary documents should concisely summarize the essential messages from the ISE and ISS that are needed to support the efficacy and safety data in the proposed product label. The process of summarizing these key points could be as straightforward as capitalizing on the similarities in format and structure of the ISE to the SCE and of the ISS to the SCS, bearing in mind that the key distinction between the integrated summaries and the clinical summaries is in the depth of the description and the supporting documentation. The numbering of the headings in the ISE/ISS

FIGURE 1

Sample transition process from ISS to SCS.

can be mapped to align with the corresponding sections of the module 2 summaries, and the most important sections of the ISE and ISS can be condensed to an appropriate length so that the entire module 2 clinical summary fits within the recommended 50 to 400 pages.

One approach for transitioning to the clinical summaries is to create discrete summary sections or summary text (including in-text TFLs, as appropriate) for each parameter or group of related parameters in the ISE or ISS. These summary sections from the ISE and ISS can then become the text for many, if not most, of the corresponding sections of the SCE and the SCS, thereby minimizing the need for new writing and TFL programming. Cross-references within each section of the SCE and the SCS can refer back to the ISE and ISS for more detailed information. This approach can help applicants meet aggressive timelines for the preparation of the clinical summaries. Figure 1 provides an illustration of a transition from the deaths section in the ISS to the corresponding section in the SCS.

As a general rule, the approach of using summary sections or summary text in the integrated summary documents to create the clinical summaries can lead to efficiencies in the writing process. For example, while the ISS will typically include a comprehensive assessment of drug safety by age (including the pediatric and geriatric subpopulations), the corresponding section in the SCS may be very brief if no differences in safety were observed between younger patients and older patients. In fact, the SCS may only require summary text such as "there were no differences in adverse events, deaths, other SAEs, or withdrawal AEs among patients less than 65 years of age compared with patients 65 years of age and older" (Figure 2).

There may, however, be discrete sections of the ISE or ISS for which the results are so critical to the understanding of the drug and support of the label that a similar level of detail is also warranted in the SCE or the SCS. Yet there is no overarching principle to summarize every issue in the SCE/SCS that appears in the ISE/ISS, as it is only these latter documents that are designed to be the primary location for in-depth analyses and discussion of more detailed topics. Thus, in transitioning from the ISE/ISS to the SCE/SCS, applicants must take care not to overwrite (nor underwrite) the clinical summaries; rather, they should find the appropriate balance between summarizing the core of the efficacy and safety analyses while providing sufficient detail of the drug's most salient aspects. This process of transitioning from the ISE to the SCE and from the ISS to the SCS is perhaps more of an art than a science, as it is difficult to provide more specific guidance given that every drug is unique.

There may be situations where the applicant has prepared a non-US submission without an ISE or ISS prior to filing a US NDA or BLA. In these instances, applicants typically conduct integrated analyses to assess efficacy and safety of the new drug (eg, program tables, review listings, analyze results, etc), and present a summary of these results in the SCE and SCS. However, they often skip the step of creating a formal ISE and ISS document. As previously stated, for purposes of a US submission, the applicant must meet the requirements specified in 21 CFR 314.50(d)(5)(v and vi). To fulfill these requirements, applicants can use the SCE and SCS documents as a foundation for creating the formal ISE and ISS documents. The ISE and ISS should include additional text, in-text TFLs,

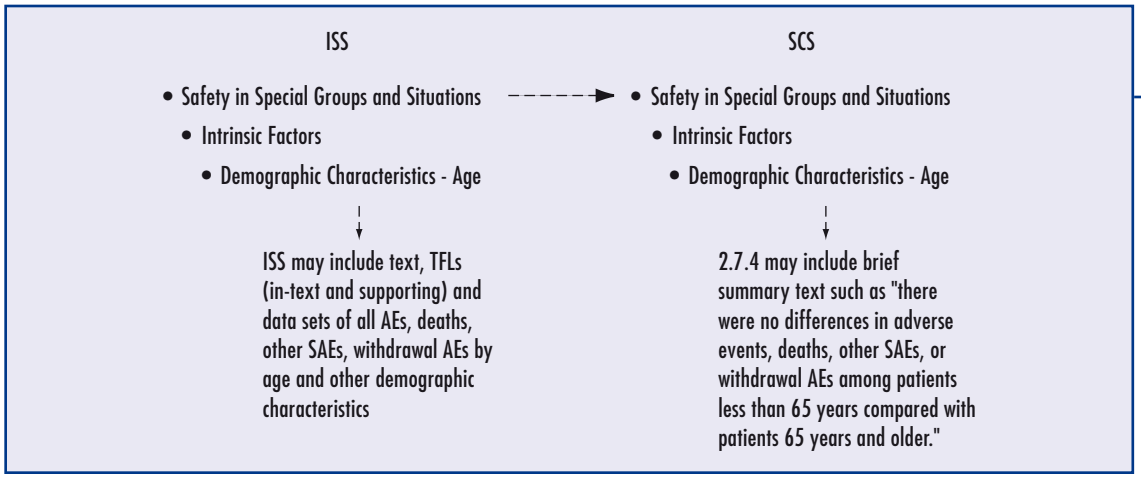

FIGURE 2

Sample transition from ISS analysis of safety by age to the corresponding section in the SCS.

end-of-text TFLs, data sets, narratives, and appendixes to provide sufficient evidence that explicitly supports the summary statements contained in the SCE and SCS. The ISE and ISS documents may also contain other analyses that the applicant did not consider sufficiently important to warrant inclusion in the SCE and SCS. Thus, applicants who have thoroughly analyzed their efficacy and safety data in an integrated fashion will be well suited to expand the SCE and SCS into an acceptable ISE and ISS.

CONCLUSION

Since the adoption in 2000 of the CTD format for marketing applications, there continues to be significant confusion regarding the similarities and differences between the US-required ISE/ISS and the CTD module 2 summaries of clinical efficacy and safety. As applicants have worked toward bringing important drugs to market more quickly, many have attempted to use the SCE and the SCS alone to fulfill the US regulatory requirements for an ISE and ISS, arguing that it is redundant to submit a separate ISE and ISS in addition to the module 2 clinical summaries. Consequently, FDA has observed an increase in the number of NDAs that do not contain detailed and fully comprehensive integrated analyses of efficacy (ISE) and safety (ISS) required by US regulations. To remedy the situation, FDA has issued numerous guidances and made podium presentations communicating the message that except in rare circumstances, NDAs should contain the ISE and ISS documents as well as the CTD SCE and SCS. Submitting detailed and fully comprehensive ISE and ISS documents not only enables applicants to comply with regulations, but may also facilitate quick and efficient preparation of the SCE and the SCS if the concepts outlined in this article are better appreciated.

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