CTD – ISS/ISE

Introduction and Summary of Issues

Robert J. Temple, M.D.
Associate Director for Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

June 21, 2006

Introduction

The CTD – a major harmonization step

- Common organization and format for all 3 regions
- Well thought out common summaries that incorporate the European Expert Report, FDA's Application summary, and presentation principles in ICH E3 and FDA's ISE and ISS documents
- Leaves room for regional differences (e.g., greater interest in comparative data in some regions)

The Issue That Still Is Being Discussed

Do you still need, for U.S. submissions, an ISS and ISE?

The answer: yes, and usually as a separate document

1. For some applications, they might fit into section 2.7 generally where, e.g., there is only one study.

2. For other applications, the ISS and ISE should be placed into module 5, although division into 2 and 5 may be possible.

Bottom line: we need what the ISS/ISE call for (they're required by regulation) and simplest is generally best.

Let me explain the ISS/ISE a little more

ISS
Integrated Summary of Safety

- A very important part of an NDA
- Required by regulation since 1985, but explained and described only in 1988, in the *Guideline for the Format and Content of the Clinical and Statistical Section of NDAs, http://www.fda.gov/cder/guidance/statnda.pdf*
- The ISS represented a revolution in our approach to safety assessment *[Temple R. The Regulatory Evolution of Integrated Safety Summary. Drug Information Journal. 1991; 25:485-92]*, even though, when you think about it, you almost have to look at safety as an integrated analysis of all data
- The ISS is misnamed; it is not a summary but an analysis

How Else Could You Do It?

- Single studies and study-by-study analyses usually cannot give the answer; you need an integrated overall view

- Large safety data base allows
  1. Study-by-study comparison of more common events
  2. Pooled estimates of common and rarer events
  3. Pooled analysis of effects in subgroups, dose response
  4. Overview of deaths and adverse dropouts

- These are NEW ANALYSES , not summaries of something else

Clin-Stat Guideline (IIH, page 32-46)

1. Overview:

   Integrates safety information from all sources (animal, clinical pharmacology, controlled and uncontrolled studies, epidemiologic data).

   - *"While other parts of the application present safety results of each study, the integrated summary is an overall analysis, examining all studies together. This allows examination of differences among population subsets not possible with the relatively small numbers of patients in individual studies, and, especially important, allows evaluation of more serious adverse effects too rare to be [seen] in single studies."*

   - *"Thus, the ISS is, in part, simply a summation of data from individual studies and, in part, a new analysis that goes beyond what can be done with individual studies."*

Clin-Stat Guideline

2. Three major elements
   a. Extent of exposure:

- a detailed description of who was exposed to the drug (diagnosis, severity of illness, concomitant illness, concomitant drugs, etc.)
- exposed to what doses
- and for how long
- Today I would add: and what assessments were carried out
- Relates to our legal requirement that applicants carry out "All tests reasonably applicable to evaluate safety."
- Implicit in asking for this information is the possibility that a reviewer could conclude there are "not enough" severely ill people, people with particular concomitant illness, people studied for long enough, or people who received the recommended dose. If no problems are seen, the drug can be said to have attained "safe passage" (Leber). This presentation allows us to consider whether exposure was sufficient to make such safe passage meaningful. Again, the reviewer would also determine whether the right studies were done

Clin-Stat Guideline

b. Assessment of Common Events

- Common events are usually easily assessed because rates can be compared in Rx and control groups.
- Not critical (usually) to approval in most cases but to proper use of the drug, so that relation to dose, demographic characteristics, renal and hepatic function is important.
- Individual study rates are of interest, but appropriately pooled rates usually give better precision and allow exploration of relation to dose, demographics, etc. Differences between studies may, however, be informative and need to be examined.
- While this analysis requires effort, it is, in a sense, always successful. These rates and subset effects can be found (exceptions: trials often fail to detect such adverse effects as abnormal sexual function and impaired cognition unless special efforts are made).

Clin-Stat Guideline

c. Serious events and the search for the “needle in the haystack.”

- Except for situations in which substantial toxicity is acceptable (cancer drugs, anti-virals) if a serious toxicity of a drug is recognized, the NDA probably would not have been submitted.
- But we know that sometimes important ADRs are missed during development, or are seen but not appreciated.
- Review of total data base is a search for the severe toxicity, “needle in a haystack,” without knowing whether there is a needle or what it looks like.
- A critical part of the search is looking at deaths and adverse dropouts, where unexpected important adverse effects should be found.

Clin-Stat Guideline

c. Search for the “needle” (cont.)

- We are good at looking for events drugs have caused in the past, or at least we eventually get good at them.
  - Relatively recently appreciate ominous nature of transaminase elevation accompanied by elevated bilirubin, so now search for that combination.
  - Now appreciate import of prolonged QT.

- Before we understand, we need to look for things we haven’t appreciated yet, and the place to look is within the deaths and adverse dropouts, particularly at events considered intercurrent illness, because anything really important should show up there.

  Recent example: *an Alzheimer’s drug caused proximal weakness, and serious breathing difficulties. This was not recognized by sponsor, yet was critical reason for NA*.

Clin-Stat Guideline

c. Search for the “needle” (cont.)

- This means that the ISS will need to present and discuss those patients (deaths and adverse dropouts) in detail.
- Some deaths, of course, are expected and will not merit close analysis, but many others will.
- The ISS asks that the location of narratives be given (i.e., narratives can be in study reports), but suggests that it might be good to put all the narratives in the ISS

Also, of course, there are CRFs available for all deaths and dropouts.

Clin-Stat Guideline

- When you've assessed the adequacy of exposure,
- Classified and analyzed the common events, and how they were assessed
- And searched the serious events and deaths and dropouts (including review of narratives and CRFs) for possible problems,
- You (the reviewer) have done all you can !
  You are finished, at least with the analysis – you still have to reach conclusions.
  That is a very good thing to know

Comment : the ISS is not as good as it should be in describing the overall approach to safety evaluation (e.g., how liver injury, QT prolongation, cataract development were assessed)

- Module 2.7.4 of the CTD does this better!

Detailed Analyses

A full description of the detailed analyses called for in the ISS is "beyond the scope" of this discussion, but:

- They are numerous, with many attached tables, and not all will be productive or worthy of a display in a summary document.
- It is important, for example, to place narratives of deaths and dropouts somewhere (in an ISS, for example) for review but many will prove uninformative and it would not be useful to put them in a summary.
- Many analyses (of ADR rates, for example) will be presented in alternative ways, e.g., with various poolings and study by study, will be accompanied by statistical presentations, etc., not all of which will be needed in detail in a summary.

ISS vs. Clinical Summary

- [illegible] is a fairly detailed Clinical Su[illegible] (Section 2.7, 50-400 pages, excluding attached tables). But a summary is not an ISS.

- There is a clear distinction between the description of a study in the Summary of Results of Individual Studies (2.7.3.2) and the full report of a study (ICH E-3), found in module 5. The summary should be relatively brief (like an abstract in a journal).

- In sum, there is a clear distinction, when considering effectiveness studies, between the SUMMARY OF A STUDY and the FULL REPORT of a study. A similar distinction applies to the overall analysis of safety.

ISS vs. Clinical Summary

- [illegible]afety (2.7.4) has all of the se[illegible]SS (actually better than current ISS because it was constructed to be similar to the ICH E3 document) and is very detailed, but it will not be a complete ISS in most cases (few narratives, selected analyses and tables, e.g.), and will usually not fit into a Clinical Summary intended to total 400 pages.

- It is completely acceptable to use the headings and sections from the CTD, instead of those from the Clin-Stat guideline to construct the ISS.

- By analogy with the reports of individual studies the Clinical Summary contains the essential safety conclusions and analyses but it is not the full ISS study report, which is contained in module 5, and would usually be distracting if shoehorned into the Summary.

Need for Both Documents

- If the full unabbreviated scope of an ISS can fit comfortably into the Clinical Summary without undermining the summary concept, a rare occurrence, then placing it there is fully acceptable. It may also be possible to put certain expanded analyses in module 5 (section 5.3.; 5.3 is there specifically for such analyses) with the bulk of the presentation in module 2, but again, dividing a single overall document may be distracting.

- But leaving out parts of the ISS to squeeze the material into a summary document serves no one's interests, can only lead to later questions and violates the regulations, which call for a full ISS.

- Given typical length of ISS (and ISE) - hundreds of pages - they do not seem easily fitted into a 50-400 page Clinical Summary; and trying to do so can interfere with the whole point of the summary.