DRUG INFORMATION ASSOCIATION

42nd Annual Meeting

ISE/ISS Analyses: Clarity in a CTD or eCTD –
Clinical Reviewer Perspective

Philadelphia 2006

Armando Oliva, M.D.

Associate Director for Policy

Office of New Drugs

CDER

FDA

Objectives

- How does the Clinical Reviewer use the ISS/ISE?
- The difference between a summary and an integrated analysis
- How to submit the ISS/ISE: EXAMPLES

Use of the ISS/ISE

- IT VARIES
- Some read it first
- Some read it last (*i.e.*, after reviewing individual study reports and clinical data)

Why Read It First?

- Serves as a good detailed integrated description of the clinical section of the application
- Can give a comprehensive “overall picture” or sense of the clinical development program with regard to safety or efficacy; its strengths and weakness
- Helps identify which studies require more in depth review

Why Read It Last?

- Desire to review the individual studies first and do his/her own independent integration of the results

- ISE/ISS later used to compare the reviewers integrated safety and efficacy findings with those of the applicant

ISE and ISS

- Are misnomers!
- Really should be called and considered as ***Integrated Analyses*** of Efficacy and Safety

Summary vs. Integrated Analysis

Summary	Analysis
High Level Overview	Detailed, In Depth Discussion
	Text Supporting Tables/Appendices Datasets
	Can Be Very Long

Summary vs. Integrated Analysis

Summary

Text

Integrated Analysis

(ISE / ISS)

Text

Tables & Appendices

Datasets

Remember

- ISE and ISS are still required by regulation and must be included in the CTD or eCTD:
  - ISE: 21 CFR 314.50 (d) (5) (v)
  - ISS: 21 CFR 314.50 (d) (5) (vi) (a)

ISE & ISS

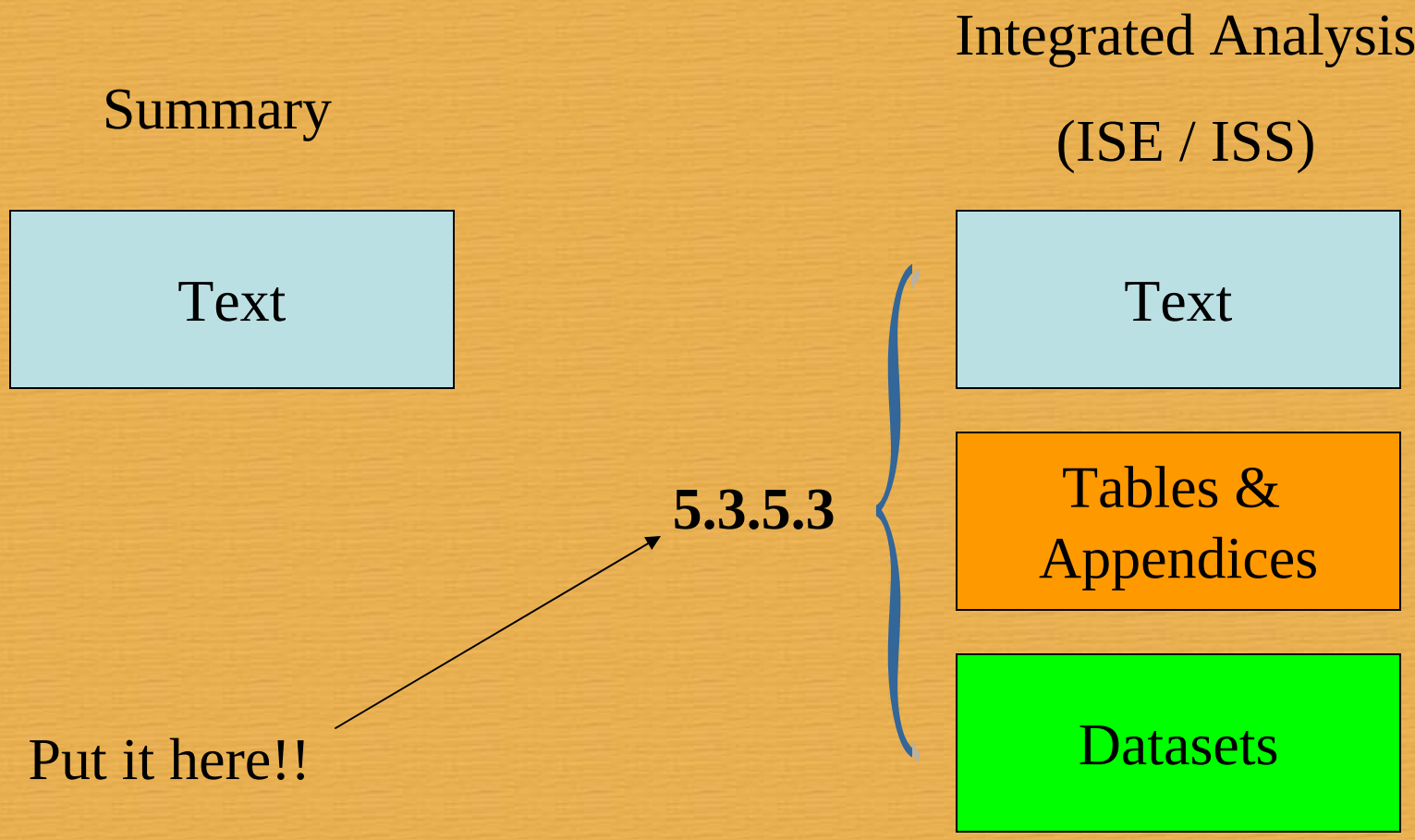
- *Question:* Where in the CTD do integrated analyses of more than one study go?

- *Answer:* Module 5.3.5.3 (ICH M4E)

CTD: Module 5, Section 5.3.5.3

5.3.5.3 Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses)

Summary vs. Integrated Analysis



Module 2

- ***Question:*** If ISE and ISS go in 5.3.5.3, what goes in Module 2 (2.7 – Clinical Summary)?
  - 2.7.3: Summary of Clinical Efficacy
  - 2.7.4: Summary of Clinical Safety
- Remember the recommended size limitation of 2.7 is 50-400 pages (ICH M4E FAQ#4)

Module 2

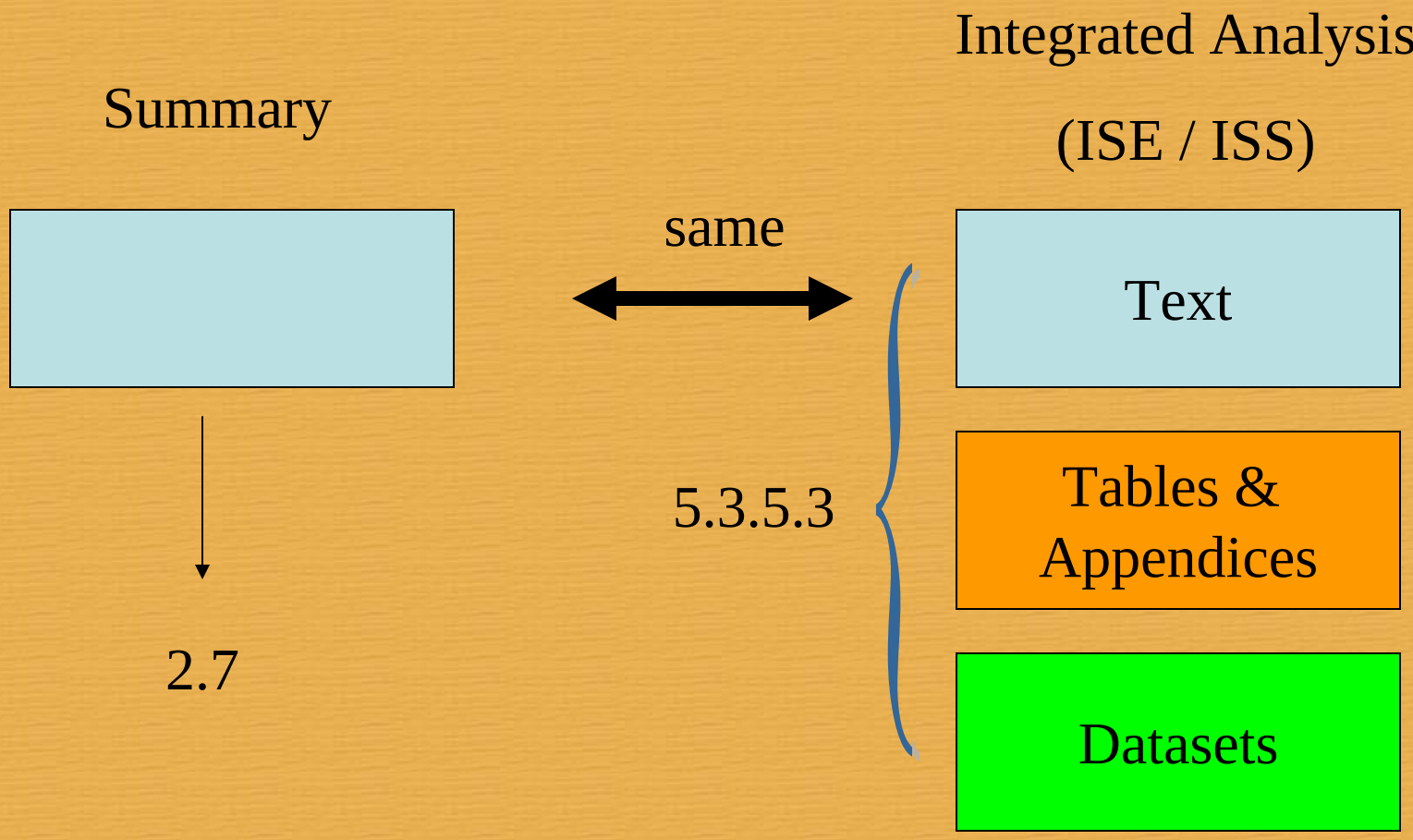
- *Answer:* the Clinical Summary is a true summary:
  - Brief: 50-400 pages
  - Text only (no large section of supporting tables and appendices*)
  - No datasets
  - Fulfills the regulatory requirements for a Clinical Summary described in 21 CFR 314.50 (c)(2)(viii)

Making Life Easier

- *Question:* How does one recycle information already contained in 5.3.5.3 for module 2?

- *Answer:* To the extent that the text portion of the ISE/ISS also meets the requirements of Module 2 (as described in ICH M4E), also include it in Section 2.7

Summary vs. Integrated Analysis

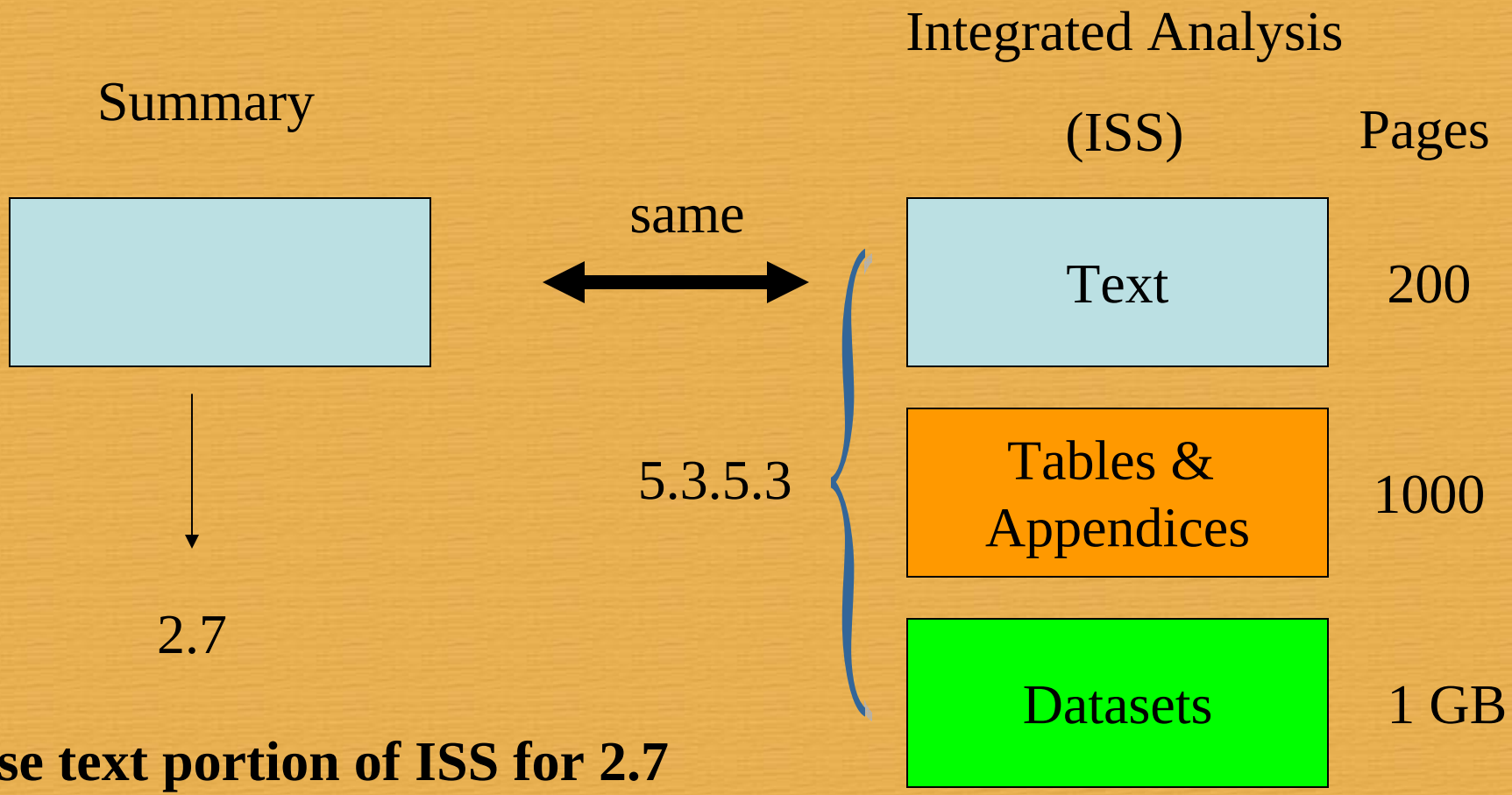


Making Life Easier

- *HINT:* When writing the text portion of the ISE/ISS in 5.3.5.3, use the headings for sections 2.7.3 and 2.7.4.

- This way, these portions of the ISE/ISS can easily be recycled for module 2 when appropriate.

EXAMPLE 1:

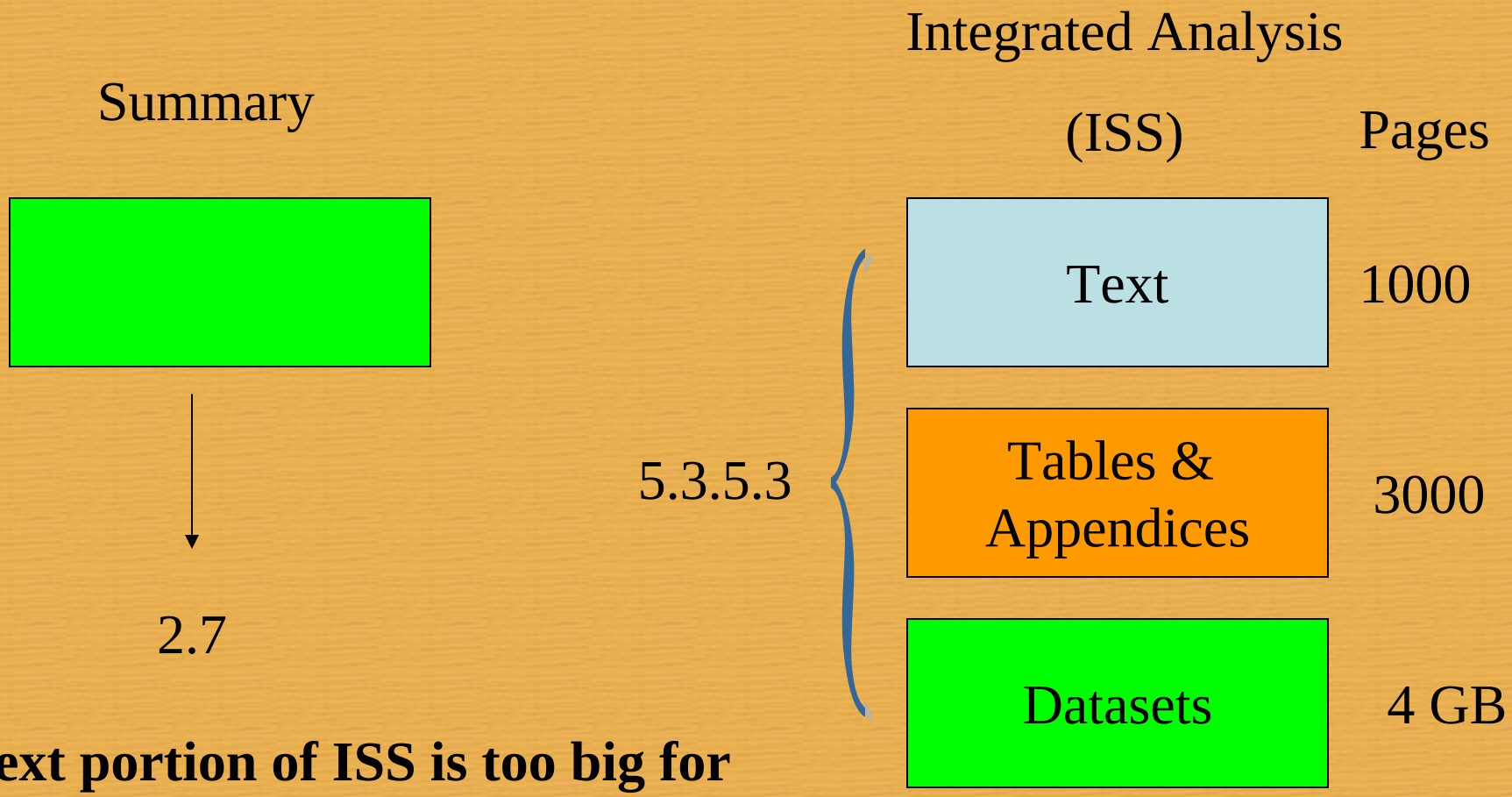


Use text portion of ISS for 2.7

One Caveat

- The situations where the text portion of the ISS can also function as the clinical summary are **uncommon** in our experience
  - e.g. safety and effectiveness derived primarily from a single study
- More often, the text portion of the ISS is too big for module 2 – not a true summary!
- Text portion of ISE more often can fit in module 2

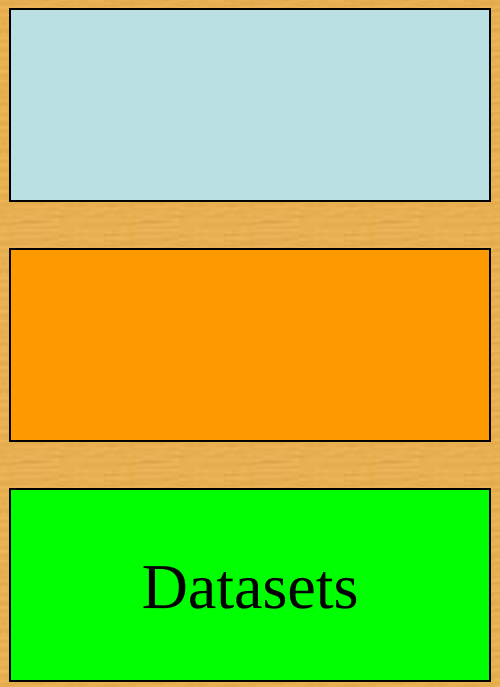
EXAMPLE 2:



Text portion of ISS is too big for module 2; needs to be summarized

EXAMPLE 3:

Summary (2.7.4)



Pages

1000

3000

4 GB

5.3.5.3

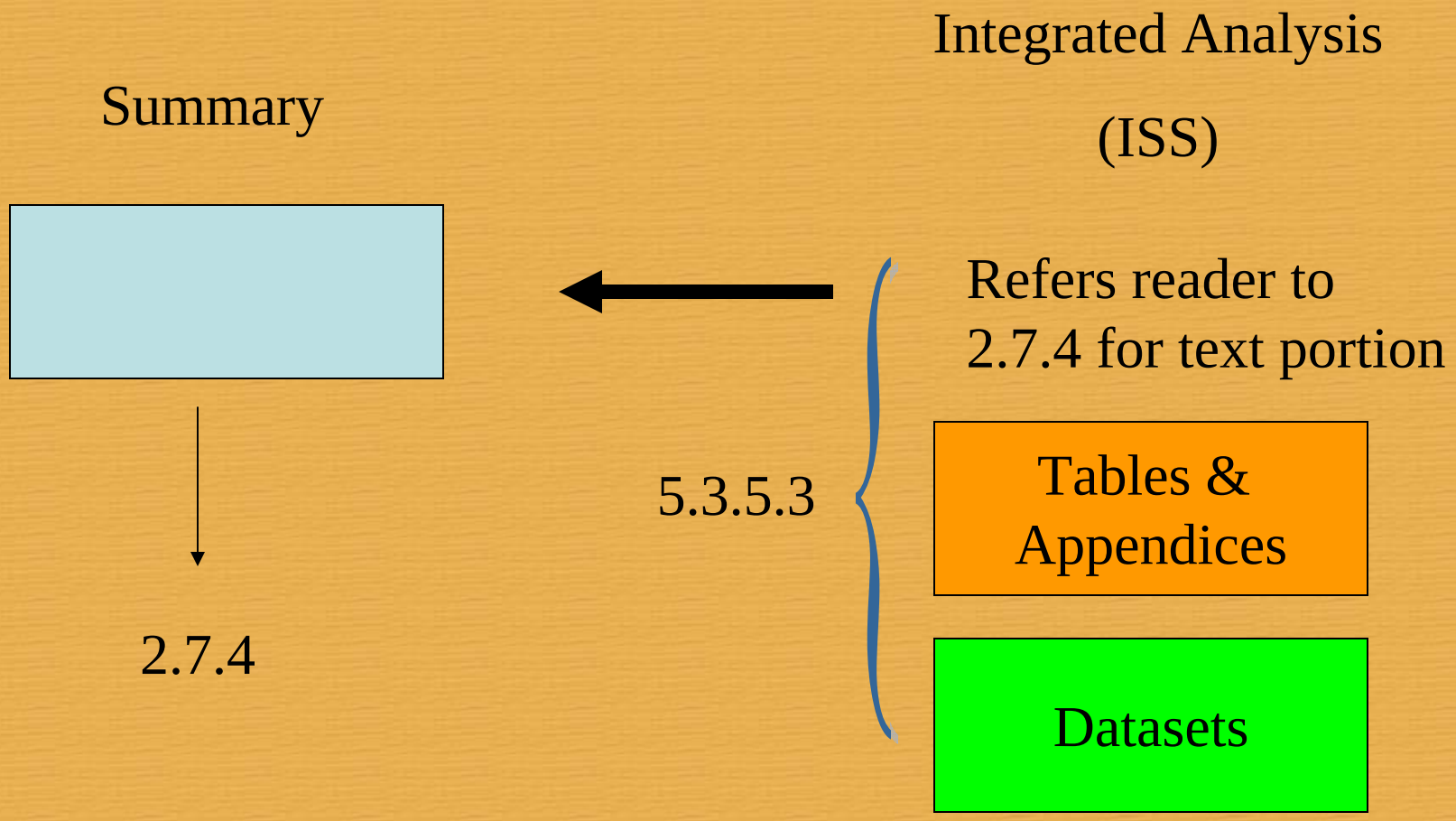
Nothing Submitted

ISS incorrectly submitted in module 2; no true "Clinical Summary" submitted … possible RTF

Paper CTD Considerations

- *Question:* When the text portion of the ISS (or ISE) located in 5.3.5.3 also serves as a true summary for module 2, should it be submitted twice?
- *Answer:* Check with review division. Some will appreciate a 2nd copy for convenience.
- IMPORTANT: If submitted only once, the corresponding section where it is missing should refer the reviewer to its correct location.

Paper CTD Example

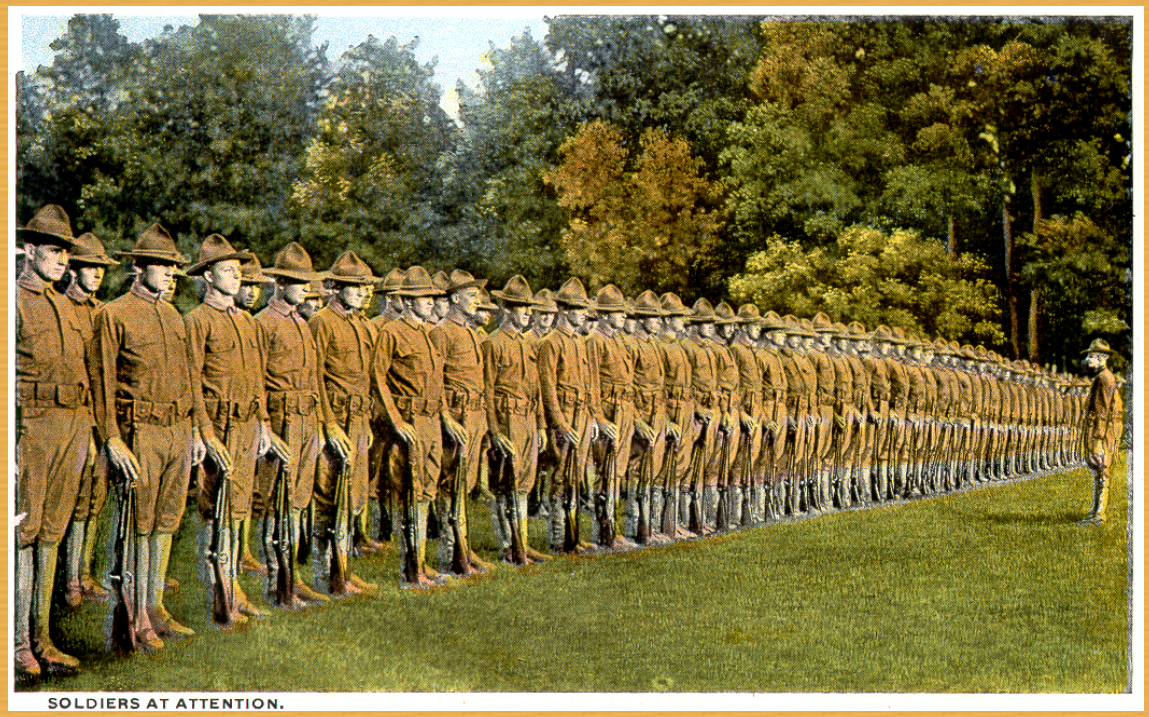


eCTD Considerations

- *Question:* When the text portion of the ISS/ISE located in 5.3.5.3 also serves as true summaries for module 2, should it be submitted twice?
- *Answer:* No. Submit only once but reference it in both locations (i.e., provide two leaf elements)

Conclusions

- ISE/ISS are still required components of the CTD/eCTD submitted to the U.S. (21 CFR 314.50)
- They are misnomers: are really *integrated analyses*
- They go in 5.3.5.3
- The text portion of the ISE/ISS can be reused for 2.7 if it meets the requirements for a summary according to ICH M4E.
- No datasets in module 2!
- Remember the recommended size restrictions for 2.7



SOLDIERS AT ATTENTION.

Armando Oliva, M.D.

(301) 796-0700

armando.oliva@fda.hhs.gov