DRUG INFORMATION ASSOCIATION

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ISS/ISE: Where Do They Fit in the CTD/eCTD?

Justina A. Molzon, M.S. Pharm., J.D.

Associate Director for International Programs

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Session 317

Medical/Scientific Writing Track

Learning objectives

At the conclusion of this session, participants should be able to:

1. Differentiate between ICH guidelines and FDA requirements for the CTD/eCTD.
2. Identify the goals of the CTD/eCTD for both industry and regulators.
3. Identify strategies to include the ISS/ISE in the CTD and eCTD submission formats.

I C H

INTERNATIONAL CONFERENCE ON
HARMONIS/ZATION
of
Technical Requirements
for the Registration of
Pharmaceuticals for Human Use

http://www.ich.org

Hosted by ICH Secretariat

IFPMA-Geneva, Switzerland

A Unique Approach

- ICH was created in 1990
- Agreement between the EU, Japan and the USA to harmonize different regional requirements for registration of pharmaceutical drug products
- Unique because joint effort by regulators and associated pharmaceutical industry trade associations

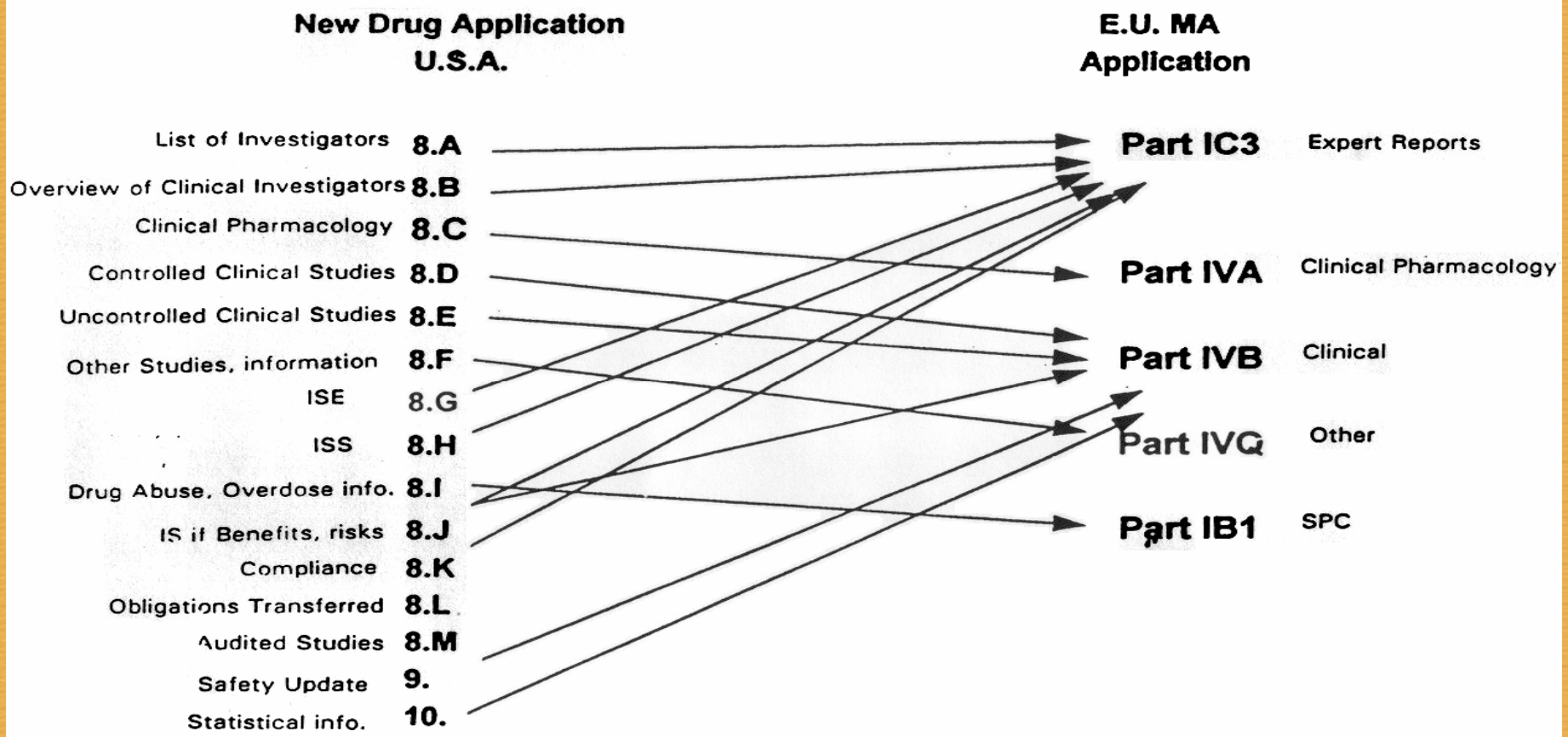
ICH Objectives

- Identification and elimination of the need to duplicate studies to meet different regulatory requirements
- More efficient use of resources in the R&D process, as a consequence
- Quicker access for patients to safe and effective new medicines

Harmonized Guidelines

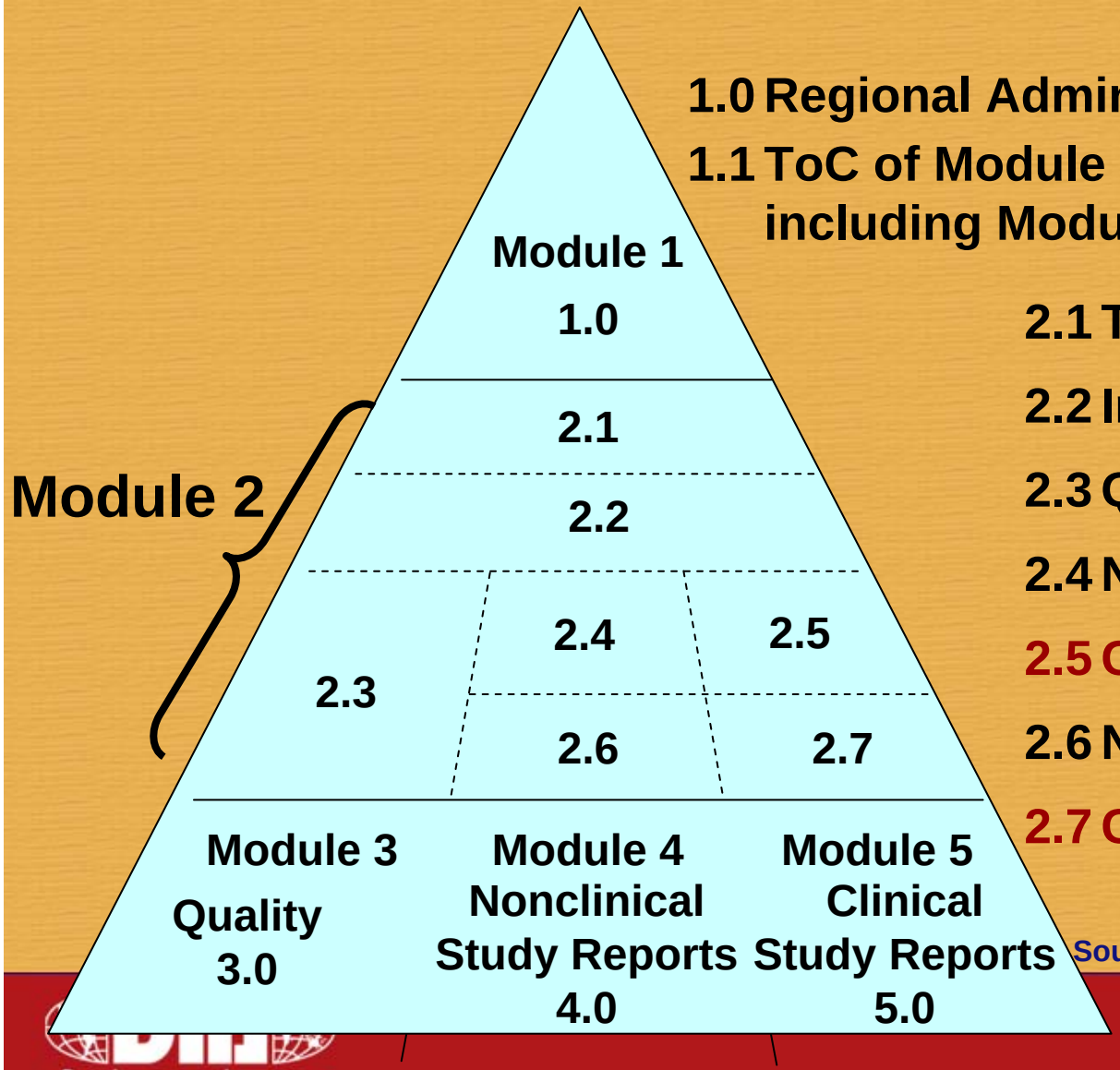
- **Efficacy** - 13 topic headings/18 guidelines
- **Safety** - 8 topic headings/16 guidelines
- **Quality** - 9 topic headings/25 guidelines
- **Multidisciplinary** (Regulatory Communications)
  - **Medical Dictionary** - MedDRA
  - **Electronic Standards** - ESTRI, E2B
- In 1996 ICH industry representatives proposed assembling the information generated by these harmonized guidances in the same order
- Goal was to decrease the amount of time and staff needed to assemble and disassemble documents for submission to ICH regions

Table of Contents Comparison



(Human PK, BA also in Part 6 of US NDA)

Common Technical Document



1.0 Regional Administrative Information

1.1 ToC of Module 1 or overall ToC, including Module 1

2.1 ToC of the CTD (Mod 2,3,4,5)

2.2 Introduction

2.3 Quality Overall Summary

2.4 Nonclinical Overview

2.5 Clinical Overview

2.6 Nonclinical Summary

2.7 Clinical Summary

Source: ICH Implementation Coordination Group

Format vs. Content

- The CTD provides a common format for the submission of information to regulatory authorities in the three ICH regions.
- However, the CTD does not address the content of submissions.
  - Regional requirements (ISS/ISE)
  - Applicants preferences
- Dossier using the CTD format (Modules 2 to 5) will not be identical for all ICH regions

July 1, 2003

CTD mandatory in the EU and Japan

- **"Highly Recommended"** by FDA
- ICH documents have always been considered GUIDANCE by FDA
- Good Guidance Practice (GGPs)
  - Final Rule September 19, 2000
  - GGPs require that the CTD not be mandatory
- Due to Regulation--Not an indication of lack of commitment to ICH or the CTD
- Submissions indicate that sponsors are following this recommendation

CTD Major Issue
Integrated Summary of Safety
Integrated Summary of Efficacy

- The name ”summary” has caused great confusion
- Not a *summary* but an *integrated analysis*
- Critical components of the safety and efficacy review and expected to be part of FDA submission.

CTD- Efficacy Question # 10

- ***Integrated Summary of Safety and Effectiveness--****Does the*

  CTD section on safety in Module 2 replace the section under 21 CFR 314.50(d)(5)(v)-(vi) calling for integrated summary of safety and effectiveness (ISS/ISE)?

ANSWER

- The ISS/ISE are critical components of the safety and effectiveness submission and expected to be submitted in the application in accordance with the regulation. FDA's guidance *Format and Content of Clinical and Statistical Sections of Application* gives advice on how to construct these summaries. Note that, despite the name, these are integrated analyses of all relevant data, not summaries.

- The Clinical Safety sections of the CTD follow approximately the outline of the sections of the ISS/ISE, although they are somewhat modified by experience with ICH E-3 (*Structure and Content of Clinical Study Reports*). The CTD Clinical Overview and Summary in Module 2 will not usually contain the level of detail expected for an ISS. It may contain the level of detail needed for an ISE, but this would need to be determined on a case-by-case basis.

- If the requirements of 21 CFR 314.50 can be met for a particular application by what is in the CTD Module 2 summary, the CTD Module 2 section ***would*** fulfill the need for an ISS/ISE. In some cases, it will be convenient to write much of what is needed in the CTD Module 2 with appropriate appendices in Module 5. In other cases, the ISS/ISE would be summarized in Module 2, with detailed reports in Module 5.
- Any questions about these matters can be raised with the reviewing division.

Updated CTD-E Q&A #10

- Based on experience with CTD/eCTD submissions
- Language submitted to ICH Secretariat for discussion with ICH Steering Committee
- Discussed during ICH SC meeting held in Yokohama June 8-9, 2006
  - Decided that since this is a US FDA requirement a link from current Q&A to CDER website for updated information was appropriate

Today's Session

- Will share ISS and ISE analysis placement tactics various sponsors have used successfully and unsuccessfully
- Objective is to help you understand how the information should be correctly submitted in CTD/eCTD
- Information presented will be posted on CDER website with link to current Q&A

Session 317—Medical Writing Track

- Background on CTD Efficacy and ISS/ISE
  - Dr. Robert Temple
    - Director, Medical Policy, CDER
- Overview of CTD Efficacy and ISS/ISE
  - Dr. Armando Oliva
    - Associate Director for Policy, Office of New Drugs, CDER
- eCTD Efficacy Submission Format
  - Gary Gensinger
    - Director, Regulatory Review Support Staff, Office of Business Process Support, CDER