TC001496A

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Course Materials

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Implementing the FDA Guidance on the Integrated Summary of Effectiveness

by Joshua Sharlin, Ph.D.

Sharlin Consulting

Date: Tuesday, August 17, 2010

Time:

1:00pm – 2:30pm	**Eastern Daylight Time** (GMT/UT 1700)
12:00pm – 1:30pm	Central Time
11:00am – 12:30pm	Mountain Time
10:00am – 11:30am	Pacific Time

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Implementing the 2008 FDA Guidance on the Integrated Summary of Effectiveness

A discussion of FDA's current recommendations on the ISE section of a new drug or biologic submission.

An FOI Services, Inc Teleconference

Tuesday, August 17, 2010
1:00pm - 2:30pm EDT (GMT – 4)

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The 2008 FDA guidance "Integrated Summary of Effectiveness" is at:

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf

Table of Contents

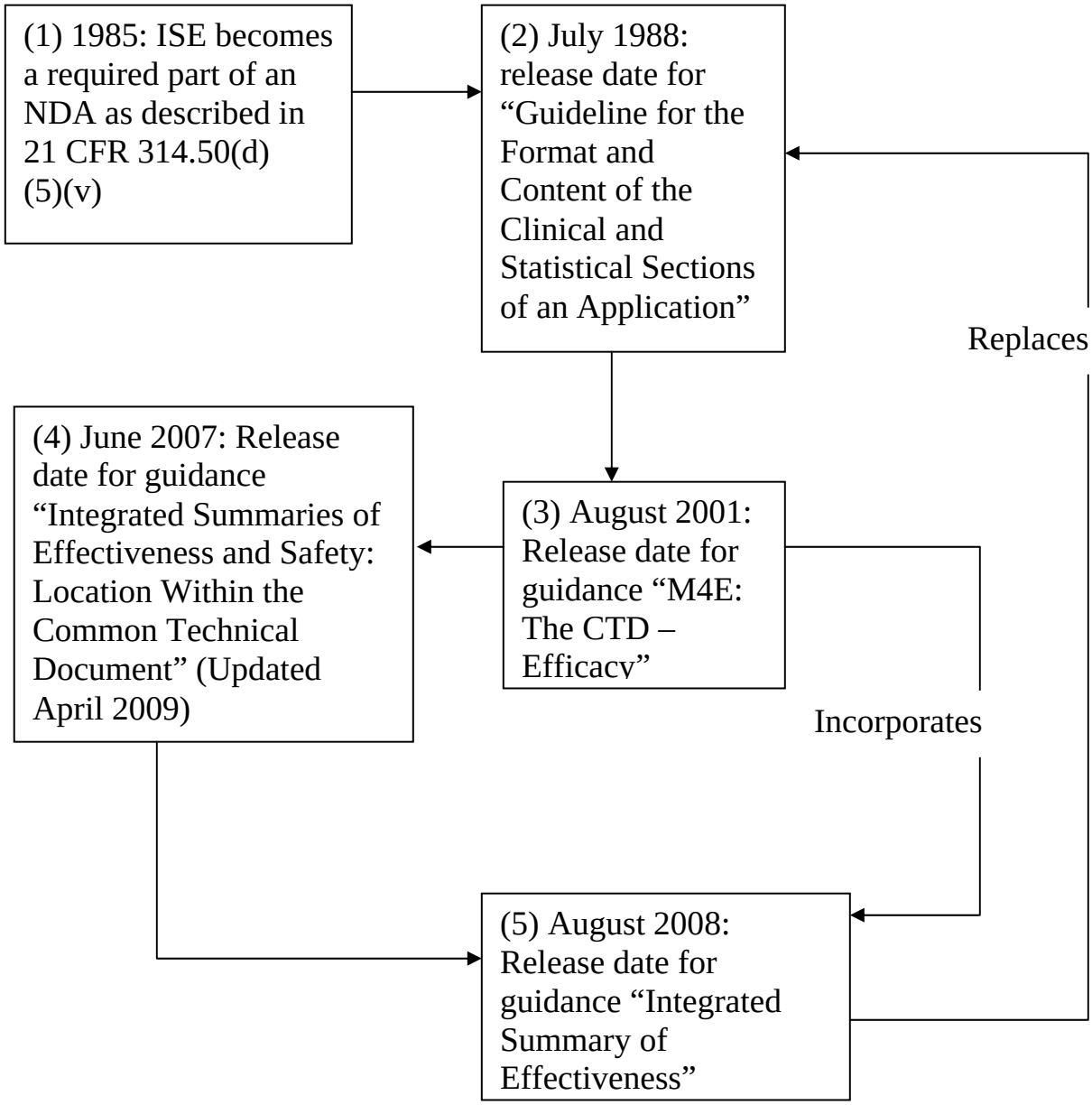
Joshua Sharlin's Credentials

1. Dr. Sharlin's resume is at the end of this handout
2. Summary of credentials:
   a. Former FDA statistical reviewer and reviewer that examined safety and efficacy
   b. Expert in writing and reviewing protocols, study reports and SOPs
   c. Authority on regulatory affairs, SAS programming, and auditing
   d. Has helped numerous FDA-regulated companies improve their compliance

Outline of This Presentation

1. History of Integrated Summary of Effectiveness (ISE) recommendations
2. Discuss applicable regulations in the *Code of Federal Regulations* (CFR)
3. Location of the ISE in a submission
4. Examine FDA reviewers' requirements for review content
5. Discuss the seven ISE required sections
6. Present next steps

History of ISE Requirements & Recommendations



Differences between the 1988 and 2008 ISE Guidances

	1988 Version	2008 Version
1	Overview	Background and overview of clinical efficacy
2	Studies that fulfill requirements for an adequate and well-controlled study	Tabular results of individual studies
3	Comparison and analysis of results of all controlled trials	Comparisons and analyses of efficacy results across studies
4	Results of uncontrolled studies	Demographics of efficacy study populations
5	Analysis of dose-response or blood-level response information	Efficacy results
6	Analysis of responses in subsets of the overall population	Analysis issues
7	Evidence of long-term effectiveness, tolerance and withdrawal effects	Integrated data analyses
8		Comparison of results in subpopulations
9		Analysis of clinical information relevant to dosing recommendations
10		Persistence of efficacy and/or tolerance effects
11		Exploratory investigations

Date	Versions of ISE Guidance
1988	Guideline for the Format and Content of the Clinical and Statistical Sections of An Application
	Section G (pages 28 to 32). Integrated Summary of Effectiveness Data
2008	Integrated Summary of Effectiveness, Guidance for Industry. August 2008, 13 pages.

ISE Requirements for an NDA in 21 CFR 314.50(d)(5)(v)

1	PART 314 – APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG
2	Subpart B--Applications
3	Sec. 314.50 Content and format of an application.
4	Applications and supplements to approved applications are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section…
5	(d)*Technical sections.* The application is required to contain the technical sections described below. Each technical section is required to contain data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the application or whether grounds exist under section 505(d) of the act to refuse to approve the application. The required technical sections are as follows:
6	(5)Clinical data *section.* A section describing the clinical investigations of the drug, including the following:
7	(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended. The effectiveness data shall be presented by gender, age, and racial subgroups and shall identify any modifications of dose or dose interval needed for specific subgroups. Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients with renal failure or patients with different levels of severity of the disease, also shall be presented.

Five Required Elements of ISE Content

This is a paraphrasing of 21 CFR 314.50(d)(5)(v), reprinted on the previous page.

1. For each of your product's claims, present an analysis and synthesis using all data to demonstrate substantial evidence of effectiveness

	From: 21 CFR 314.126 Adequate and well-controlled studies (This is a partial reprint of the regulations.)
1	Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is ''substantial evidence'' to support the claims of effectiveness for new drugs.
2	(b) An adequate and well-controlled study has the following characteristics:
3	(1) There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis…
4	(2) The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.
5	(3) The method of selection of subjects provides adequate assurance that they have the disease or condition being studied,
6	(4) The method of assigning patients to treatment and control groups minimizes bias
7	(5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data.

Five Required Elements of ISE Content (page 2)

2. For the dosage and administration section of your product's label, present supporting information. Also present data to support your recommended dosage and dose interval.

	From: 21 CFR 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in 201.56(b)(1) (This is a partial reprint of the regulations.)
1	(3)*2 Dosage and administration* . (i) This section must state the recommended dose and, as appropriate: (A) The dosage range, (B) An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness, (C) Dosages for each indication and subpopulation, (D) The intervals recommended between doses, (E) The optimal method of titrating dosage, (F) The usual duration of treatment when treatment duration should be limited, (G) Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food effects), (H) Modification of dosage needed because of drug interactions or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease), (I) Important considerations concerning compliance with the dosage regimen, (J) Efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites, if established and clinically significant. Information on therapeutic drug concentration monitoring (TDM) must also be included in this section when TDM is necessary.

Five Required Elements of ISE Content (page 3)

3. Present effectiveness data for the following patient population subgroups: for each gender, for each race, and for age subgroups

4. Regarding product dose or dose interval, provide information about patient population subgroup differences

5. Regarding product effectiveness, include all necessary data about differences between any patient population subgroups (e.g., patients with renal failure or different levels of disease severity)

ISE is a Recommended Part of a BLA

1. An ISE is a recommended, not a required, part of a BLA

From: Integrated Summary of Effectiveness Guidance, August 2008
Line 24. Although there are no corresponding regulations requiring an ISE for BLA submissions, applicants are encouraged to provide these analyses in their applications.

BLA – Biologics License Application

The ISE is *Not* a Summary

1. Although "summary" is in the title of an Integrated Summary of Effectiveness (ISE), the actual content of an ISE is an overall synthesis and analysis of information from all studies.

	Reference 1.
	From: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document. **April 2009 Guidance**
1	Page 1. However, the ISE and ISS are <u>not summaries</u> but rather <u>detailed integrated analyses</u> of all relevant data from the clinical study reports that belong in Module 5.

	Reference 2.
	From: Integrated Summary of Effectiveness. **August 2008 Guidance**
1	Line 95. Although one of the goals of the ISE is to summarize the available effectiveness data, the ISE primarily is an integrated analysis of these data, going <u>beyond a simple summary</u>. .

NDA Content Can Follow the CTD or FDA Form 356h

1. The content of a paper submission can follow the organization of either FDA Form 356h or the CTD (Common Technical Document)

2. FDA Form 356h, "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use"
    a. The form references 19 sections of a submission
    b. Section #8, Clinical Data section, includes the ISE

3. The CTD contain regional sections and common sections divided into five modules
    a. Countries that are part of the ICH (International Conference on Harmonization) agree to accept the CTD as a submission format

4. The content of an electronic submission must follow the organization of the eCTD (electronic Common Technical Document)
    a. The CTD and eCTD have the same organization

Locate the ISE in CTD Module 5 (Clinical Study Reports)

1. For a submission that contains data from several clinical trials, put the ISE in CTD Module 5, section 5.3.5.3

	From: Page 3. Integrated Summaries of Effectiveness and Safety: Location Within the CTD **April 2009 Guidance**		
	CTD Section	**Requirement in the CFR**	**Comment**
1	2.5 Clinical Overview (~30pages)		
1.1	2.5.4 Overview of Efficacy	Not applicable	Not a U.S. requirement, but recommended by ICH M4E
1.2	2.5.5 Overview of Safety		
2	2.7 Clinical Summary (~50-400 pages)		
2.1	2.7.3 Summary of Clinical Efficacy	21 CFR 314.50(c)(2)(viii)	U.S. requirement for a clinical summary
2.2	2.7.4 Summary of Clinical Safety		
3	5.3 Clinical Study Reports		
3.1	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)	ISE - Integrated Summary of Effectiveness
		21 CFR 314.50(d) (5)(vi)	ISS – Integrated Summary of Safety

CTD – Common Technical Document. The CTD is the required table of contents for an electronic submission and an option table of contents for paper submissions.

Locate the ISE in CTD Module 5 (page 2)

1. The April 2009 "Location" guidance specifies that the ISE be located in CTD section 5.3.5.3

From: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document. **April 2009 Guidance**
Page 4. In general, Module 5, specifically section 5.3.5.3, Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses), is the appropriate location for the ISE and ISS. This module is designed to contain more detailed in-depth analyses, and unlike Module 2, Module 5 has no space limitation.

Placing ISE Information in CTD Module 2 Can Generate a Refuse to File

1. FDA expects your ISE information to be in CTD Module 5

2. Any other location can result in a refuse to file action

From: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document. **April 2009 Guidance**
Page 2. Generally, the Module 2 clinical summary sections (hereafter clinical summary sections) 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. Page 3. A common problem with the CTD-formatted applications is that applicants incorrectly assume that the clinical summary sections satisfy the regulatory requirement for the ISE and ISS. This assumption can result in a determination by the FDA that an application is incomplete and may result in a refusal-to-file action for the application

Refuse to file – FDA rejects your submission because it is incomplete; your application fee is not refunded.

For Small Studies, the ISE Could Be Split between CTD Modules 5 and 2 (CTD Summaries)

1. An exception to the recommendation for placing the ISE in CTD section 5.3.5.3 is allowed for small studies
2. For small studies, the ISE can be divided between two locations:
    a. CTD section 2.7.3 for the narrative portion
    b. CTD section 5.3.5.3 for tables figures and datasets

	Reference 1.
	From: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (April 2009 Guidance)
1	Page 4. In such situations, the ISE and ISS can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in section 5.3.5.3.
2	Page 4. This situation is rare but can occur if the application is small and consists of a single study or a number of small studies.

	Reference 2.
	From: Integrated Summary of Effectiveness (August 2008 Guidance)
1	Line 100. 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.

In a Paper Submission, Place the ISE in Clinical and Statistical Sections

1. For a submission table of contents, the alternative to the CTD is FDA Form 356h (Application to Market a New Drug, Biologic or an Antibiotic for Human Use).
2. Form 356h divides a submission into 19 sections
    a. Section 8 - Clinical data section
    b. Section 10 - Statistical section

From: Guideline for the Format and Content of the Clinical and Statistical Sections of an Application (July 1988 Guidance)
Page 28. H. Integrated Summary of Safety Information [21 CFR 314.50 (d)(5)(v)] The content of this section should be included in both the clinical and statistical technical sections.

Information Reviewers Require For a Statistical Review, MAPP 4000.8

1. From MAPP 4000.8 – Biostatistics New Drug Application Review Template (April 2005)
2. Statistical evaluation
    a. Evaluation of efficacy
    b. Study design and endpoints
    c. Patient disposition
    d. Demographic and baseline characteristics
    e. Statistical methodology
3. Findings in subgroup populations
    a. Gender, race and age
    b. Special subgroup populations
4. Statistical issues
5. Collective evidence

MAPP – Manual of Policies and Procedures, an internal CDER document written for use by reviewers.

Information Reviewers Require For a Clinical Review, MAPP 6010.3

1. From MAPP 6010.3 – Clinical Review Template, July 2004
2. Dose-finding information
3. Evidence of an adequate and well-controlled study (described in 21 CFR 314.126)
4. Relevant data that was not provided, creating insufficient information to reach a decision
5. Evaluation of choice of end point, including limitations
6. How study bias was minimized
7. Choice of a control group
8. Adequacy of study duration
9. Critique of inclusion and exclusion criteria
10. Regarding efficacy findings:
    a. Impact of demographic and baseline characteristics on efficacy conclusions
    b. Discuss study results that did not support efficacy claims
    c. Limitations of available data
11. Need for additional information

MAPP – Manual of Policies and Procedures, an internal CDER document written for use by reviewers.

Four ICH Guidances Related to the ISE

1. ICH E3, Structure and Content of Clinical Study Reports
2. ICH E9, Statistical Principles for Clinical Trials
3. ICH E10, Choice of Control Group and Related Issues in Clinical Trials
4. ICH M4E, The CTD – Efficacy
    a. Section 2.7.3, Summary of Clinical Efficacy
    b. August 2001 FDA/ICH Guidance for Industry, "M4E: The CTD – Efficacy" provides recommendations for the content of each part of CTD section 2.7.3

ICH – International Conference on Harmonization

CTD – Common Technical Document (Another name for a required table of contents.)

Contents of CTD Section 2.7.3: Summary of Clinical Efficacy - Comparison to ISE Guidance

1. The 2008 "Integrated Summary of Effectiveness" states on line 30: "This guidance…incorporates the conceptual framework of section 2.7.3"

2. Your actual ISE information must be placed in CTD Module 5.3, Clinical Study Reports. (see pg 4 in the April 2009 FDA guidance, "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document")

1	Module 2: Common Technical Document Summaries		
2	2.7: Clinical Summary		
3	2.7.3: Summary of Clinical Efficacy		
4	**CTD Section #**	**CTD Section Name**	**7 ISE Sections from August 2008 FDA ISE Guidance**
5	2.7.3.1	Background and Overview of Clinical Efficacy	(1) Background and Overview of Clinical Efficacy
6	2.7.3.2	Summary of Results of Individual Studies	(2) Tabular Results of Individual Studies
7	2.7.3.3	Comparison and Analyses of Results Across Studies	(3) Comparisons and Analyses of Efficacy Results Across Studies
8	2.7.3.4	Analysis of Clinical Information Relevant to Dosing Recommendations	(5) Analysis of Clinical Information Relevant to Dosing Recommendations
9	2.7.3.5	Persistence of Efficacy and/or Tolerance Effects	(6) Persistence of Efficacy and/or Tolerance Effects
10	2.7.3.6	Appendix	
11			(4) Comparison of Results in Subpopulations
12			(7) Exploratory Investigations
13	The 7-page August 2001 FDA/ICH Guidance for Industry, "M4E: The CTD – Efficacy" makes recommendations for the content of each CTD section under 2.7		

Tables and Figures in an ISE

1. Compact tables and figures should be part of the text
2. Lengthy tables should be put in an appendix at the end of the section containing the ISE (ISE Guidance, August 2008, line 492)
3. For electronic submissions, insert hyperlinks for tables

Reprint from January 1999 guidance, "Providing Regulatory Submissions in Electronic Format – General Considerations" page 10:

> Hypertext links throughout the body of the document to supporting annotations, related sections, references, appendices, tables, or figures that are not located on the same page are helpful and improve navigation efficiency. Use relative paths when creating hypertext linking to minimize the loss of hyperlink functionality when folders are moved between disk drives.

What the ISE Should Not Contain

1. Repeat information in individual study reports (ISE Guidance, August 2008, line 114)

2. Graphs, mathematical derivations or presentations of formulae in the ISE body. Instead, put this information in an ISE appendix. (ISE Guidance, August 2008, line 165)

3. Unplanned interim analyses on ongoing studies (ISE Guidance, August 2008, line 499)

Seven ISE Sections

The August 2008 guidance, "Integrated Summary of Effectiveness" recommends an ISE contain 7 sections:

1. Background and Overview of Clinical Efficacy
2. Tabular Results of Individual Studies
3. Comparisons and Analyses of Efficacy Results Across Studies
4. Comparison of Results in Subpopulations
5. Analysis of Clinical Information Relevant to Dosing Recommendations
6. Persistence of Efficacy and/or Tolerance Effects
7. Exploratory Investigations

ISE Section 1 of 7 - Background and Overview of Clinical Efficacy

1. In this section, explain why individual studies were adequate and well-controlled and how they provide evidence supporting your product's claim.

> An adequate and well-controlled study has the following characteristics: The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. (From: 21 CFR 314.126 (b)(2))

2. Discuss and compare key study characteristics among trials and, if necessary, explain inconsistent study results

3. Key study characteristics that could be discussed include:

    a. Randomization

    b. Blinding

    c. Statistical methods

    d. Choice of patient population

4. If a novel surrogate endpoint is used, explain and justify its use

ISE Section 2 of 7 - Tabular Results of Individual Studies

1. Create a table listing all relevant studies
2. Include both positive and negative results
3. Describe important study design features and critical results
4. Write an abstract for each study
5. Insert a reference to the complete study report

ISE Section 3 of 7 - Comparisons and Analyses of Efficacy Across Studies

1. The text, figures and tables used in this section should include all data that supports a product's efficacy
2. Include two types of analyses
    a. Comparison of results of individual studies
    b. Analysis based on information combined from different studies
3. Enhance the accuracy and reliability of this technical view of all submission information by adjusting for trial design factors. For example:
    a. Weighting by sample size
    b. Use covariates to adjust for quantifiable variability
    c. Stratify the patient population so that statistical analysis is more meaningful
4. Discuss any inconsistencies across studies in efficacy results or conclusions

ISE Section 3 of 7 - Comparisons and Analyses of Efficacy Across Studies (page 2)

5. In the design and execution of comparisons and analyses using all data, consider the following:
    a. Definition of the control group
    b. Duration of exposure to the product
    c. Demographics and other important characteristics of the patient population
    d. Definition and calculation of the primary endpoint
    e. Characteristics of patient dropouts
    f. Differences in statistical analyses

ISE Section 3 of 7 - Comparisons and Analyses of Efficacy Across Studies: (1) Demographic & Baseline Characteristics of Efficacy Study Populations (page 3)

1. The ISE section about demographic and baseline characteristics should include the following information gathered from all efficacy studies:

    a. Severity and duration of the disease condition before treatment began

    b. Concomitant treatments

    c. Inclusion and exclusion criteria

    d. Differences in efficacy results by age, sex, race and region (USA versus non-USA)

    e. Differences in the study population that participated in clinical trials as compared to the population that will use the product after approval

    f. Analysis of dropouts - Calculate dropouts by treatment group, categorized by time of withdrawal and include reasons for discontinuation

ISE Section 3 of 7 - Comparisons and Analyses of Efficacy Across Studies: (2) Efficacy Results (page 4)

1. Summarize and compare results from all controlled studies both favorable and unfavorable
    a. Note differences in study design (e.g., endpoint, study duration, patient population, dose, statistical methods)
    b. Emphasize the primary efficacy variable or any other variable that is measured and analyzed the same way across all studies
2. The presentation of efficacy results for all studies should employ the same methods used to report individual studies
3. Studies with the same design features (e.g., type of control, dose, duration) should be discussed together
    a. Explain any important differences in outcome
4. Report on any bridging study in this section (A bridging study demonstrates that results from a study conducted outside the US can be applied to a US population. It is designed to extend the applicability of a confirmatory study, usually to broaden the population to which the results apply.)

ISE Section 3 of 7 - Comparisons and Analyses of Efficacy Across Studies: (3) Analysis Issues (page 5)

1. Write a summary and discussion of the statistical analysis of each study
2. Present information and conclusions about the strength of your statistical evidence. For example:
    a. Consistency of findings across studies
    b. Width of confidence intervals
    c. Magnitude of p-values
3. Acknowledge inconsistent results
4. Itemize statistical issues. Discuss their impact and resolution. For example:
    a. Problems in maintaining or breaking the blind
    b. Unexpectedly high numbers of dropouts
    c. Inconsistent or unplanned methods for replacing missing values (i.e., imputation)
    d. Changing the number of patients per treatment (or any other study design modification) after study start
    e. Inflation of the Type 1 error rate caused by too many or unplanned treatment comparisons

ISE Section 3 of 7 - Comparisons and Analyses of Efficacy Across Studies: (4) Integrated Data Analyses (page 6)

1. "Integrated analyses" means "synthesizing the results of individual studies in an appropriate manner to collectively provide support for the claimed effectiveness of the study drug". (See line 292 in August 2008 guidance.)

2. Synonyms for integrated analyses include meta-analysis, analysis of pooled data, analysis of combined data

3. Characteristics of an integrated data analysis acceptable by FDA reviewers:

    a. Unless individual studies show positive results, it's unlikely that FDA reviewers will accept pooled data as evidence supporting product approval

        i. An exception is if a pooled analysis was specified in the protocol as the method for analyzing the primary efficacy variable

    b. Minimize bias by selecting studies to be combined before the trial begins. Describe the selection in the protocol.

    c. Clearly state if the decision about what studies to combine was done after the trail was completed (i.e., *post hoc*)

    d. Thoroughly describe any differences among studies to be combined

    e. Provide details about methods used to combine data

    f. Describe the logic, methods and assumptions of your statistical analysis

ISE Section 4 of 7 - Comparison of Results in Subpopulations

1. The intent of this section is improve the understanding of your product's efficacy by examining its effect on sub-populations of patients where differences in product effectiveness might be expected

2. This section should NOT be used to demonstrate a product's effectiveness in a subpopulation when overall study results were negative

3. Characteristics of sub-populations:

a. Demographic factors such as age, sex, race

b. Factors that could impact product effectiveness. For example, disease severity, prior treatment, concomitant illness or drugs, alcohol or tobacco use, body weight.

c. Regional differences for global studies

4. Conduct this subpopulation analysis using pooled data

5. Present results using tables, figures or plots

6. Clinically meaningful results merit special attention

7. Statistical tests could be necessary if the results and conclusions appear in the product's label

.

ISE Section 4 of 7 - Comparison of Results in Subpopulations (page 2)

8. Be aware of requirements described in the Pediatric Research Equity Act of 2007
   a. Applies to submissions of a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration
   b. The act requires that the safety and efficacy of the drug be assessed in all relevant pediatric populations
   c. A waiver is possible. Regulations don't necessarily apply to products intended for adults

ISE Section 5 of 7 -Analysis of Clinical Information Relevant to Dosing Recommendations

1. This section uses all study data to describe dose-response and blood level-response relationships. This includes:
    a. How to adjust the dose for an individual
    b. Suggested dose intervals
    c. Starting and maximum doses
2. Discuss any factors affecting dosing recommendations. For example:
    a. Demographic characteristics (e.g., age, sex, race)
    b. Disease state
3. Even if the dosing investigation does not produce any recommendations, report the methods and results anyway

ISE Section 6 of 7 - Persistence of Efficacy and/or Tolerance Effects

1. This section investigates treatment response over time
2. Emphasize data from studies designed to collect efficacy data
    a. Include number of subjects
3. An analysis of response over time could investigate:
    a. Consistency
    b. Relation to dose
    c. Decrease in efficacy over time (i.e., tolerance)

ISE Section 7 of 7 - Exploratory Investigations

1. Analysis of study data sometimes includes endpoints, patient populations, and pooled data NOT specifically described in a protocol or statistical analysis plan

2. Information from unplanned analyses does not meet requirements in the CFR for an adequate and well-controlled clinical study:

    a. Therefore these exploratory investigations cannot support a product's efficacy

3. However, exploratory analyses can provide useful information, for example:

    a. Ideas for additional studies (e.g., post-approval or a registry)

    b. Additional insight about an established claim (e.g., the product's effect on a newly-defined patient population)

Checklist: Mapping ISE Submission Content into the CFR

	ISE Checklist	
	Requirement from 21 CFR 314.50(d)(5)(v)	Page(s) in, or Link(s) to, your submission
1	For each of your product's claims, present an analysis and synthesis using all data to demonstrate substantial evidence of effectiveness	
2	For the dosage and administration section of your product's label, present supporting information. Also present data to support your recommended dosage and dose interval	
3	Present effectiveness data for the following patient population subgroups: for each gender, for each race, and for age subgroups	
4	Regarding product dose or dose interval, provide information about patient population subgroup differences	
5	Regarding product effectiveness, include all necessary data about differences between any patient population subgroups (e.g., patients with renal failure or different levels of disease severity)	

Key Points from this Teleconference

1. Place the ISE in Module 5 of your NDA
    a. As suggested in the April 2009 FDA guidance "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document"

2. Three sources of information about the contents of an ISE
    a. April 2009 guidance "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document"
    b. August 2008 guidance "Integrated Summary of Effectiveness"
    c. August 2001 guidance "M4E: The CTD – Efficacy"

3. General principles of ISE contents:
    a. Methods and strategies of information analysis must be specified in advance
    b. Include information that can provide insight about the subtleties of a product's effectiveness?
    c. Information that does not support your product's claim must be included
    d. Clearly present efficacy analysis using patient sub-populations

Next Steps

1. Read MAPP 4000.8 (Biostatistics NDA Review Template) and MAPP 6010.3 (Clinical Review Template)

2. Study the contents of the August 2008 ISE guidance

3. Map information in your submission to 21 CFR 314.50(d)(5)(v), the required contents of an ISE

Joshua Sharlin, Ph.D., Resume

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Summary: Dr. Sharlin has practical hands-on experience in many aspects of drug, biologic and medical device development including; regulatory affairs, protocol development, design and execution of studies, data collection, data management, data reporting, statistical analysis, software programming and validation, technical writing, and FDA compliance.

Highlights of Qualifications & Services

* FDA drug reviewer, FDA statistician, instructor for SAS Institute
* Authority in 21 CFR Part 11 compliance and assessments
* Teach audioconferences and customized onsite training classes
* Audit CROs, sponsors and vendors for FDA compliance
* Regulatory affairs and GCP compliance expert
* Write and improve SOPs

Relevant Experience & Accomplishments

FDA Compliance and Product Submission Experience

Assisted drug and device firms of all sizes in issues related to FDA approval and FDA compliance. Designed studies, performed statistical analyses, and wrote study reports for INDs, NDAs, BLAs and PMAs. Developed regulatory strategies to create a marketable product with a limited budget. Prepared and presented information to FDA reviewers. Identified and solved FDA compliance gaps especially regarding SOPs.

Responsibilities as an FDA Reviewer

While at the FDA, responsible for managed the drug review process. Instructed firms on how to proceed with drug approval. Summarized outstanding problems and issues with protocols and studies, and determined if deficiencies were adequately addressed. Authored all written communication to the sponsoring firm and integrated comments from other reviewers. Promoted the idea of a standards based electronic submission. Developed automated methods for performing quality assurance review of study data.

Data Auditing and Software Validation Skills

Audited the software development and data management practices of drug sponsors, CROs and vendors and made recommendations for how to improve the quality and speed of code development. Identified problems with data, and suggested how to minimize the negative effect on FDA review time. Reviewed and audited work for software quality and validity of statistical conclusions. Improved compliance with GCP regulations including 21 CFR Part 11.

Relevant Experience, continued

Software Development and Database Experience
Managed multi-million dollar software development projects and participated in all phases of the software development process including requirements definition, software design, development, testing and maintenance. Worked as a programmer on the Consumer Price Index (CPI). Led development of a ten million record customer database and on-line application for Marriott Hotels.

Scientific Experimentation Skills
Conceived, designed and executed scientific studies. Experienced in conducting radioimmunoassays, electrophoresis, enzyme quantification, and chromatography. Presented papers at scientific meetings and published articles in peer reviewed scientific journals.

Statistical and SAS Programming Experience
Consulted with scientists from FDA-regulated industry on calculation of sample sizes, design of studies and statistical analysis of data. Interpreted results of statistical tests. Designed, coded and tested software programs that performed statistical analysis and produced tables and listings. Taught SAS programming for SAS Institute. Improved skill and FDA compliance of SAS programmers.

Development and Delivery of Teleconferences and Onsite Training
Since 2002 have developed and presented dozens of teleconferences to thousands of individuals from hundreds of FDA regulated companies. Topics have included, 21 CFR Part 11 compliance, regulatory affairs, adverse event reporting, annual reporting, statistical analysis, SAS programming, electronic submissions, auditing and writing SOPs. Used content from presentations to teach customized in-house classes to regulatory and QA staff, statisticians, programmers and database specialists.

Employment History

1994-present	**Consultant**	Sharlin Consulting, Washington, DC
	FDA compliance expert, trainer, SAS programmer, statistician, technical writer, auditor and 21 CFR Part 11 authority.	
1992-94	**Drug Reviewer**	Food & Drug Administration, Rockville, MD
	Reviewed clinical studies and managed the drug review process.	
1989-92	**Director, Hotel Customer Information Systems**	Marriott Hotels & Resorts, Bethesda, MD
	Managed a programming staff of 21 with a $4 million annual budget.	
1981-89	**Consultant**	ORI, Inc., Rockville, MD
	Manager and programmer on software development projects for healthcare companies and federal government agencies including the National Institutes of Health (NIH).	
1977-81	**Research Scientist**	University of Georgia, Athens, GA
1975-77	**Statistician**	U.S. Dept of Agriculture, Beltsville, MD

Education

Ph.D.	Physiology	University of Georgia
M.S.	Physiology	University of Maryland
B.A.	Zoology	University of Iowa

Training Evaluation Form

TC001496

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Joshua Sharlin, Presenter – August 17, 2010

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