Integrated Summary of Effectiveness

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2015
Procedural

Integrated Summary of Effectiveness

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Tel: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
or
Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
Tel: 800-835-4709 or 240-402-7800; Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2015
Procedural

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 2

III. FORMAT AND CONTENT OF THE ISE 3

A. Listing and Brief Results of Individual Studies 4

B. Analysis of Study Designs 5

C. Overall Analysis of Effectiveness Results 7

1. Comparison of Results of Individual Studies 9

2. Pooled Analyses of Data From More Than One Study 10

D. Comparison of Results in Subpopulations 11

E. Analysis of Clinical Information Relevant to Dosing Recommendations 13

F. Time Course of Effect, Persistence of Effect and/or Tolerance, Distribution of Responses . 13

G. Exploratory Investigations 14

GLOSSARY 15

REFERENCES 16

Contains Nonbinding Recommendations

Integrated Summary of Effectiveness Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes the recommended content of the integrated summary of effectiveness (ISE) for inclusion in a new drug application (NDA) or biologics license application (BLA).[2] Although there are no regulations requiring an ISE for BLA submissions, applicants are encouraged to provide an ISE because it represents an opportunity to present a coherent analysis and presentation of the drug's benefits.

The recommendations in this guidance reflect the FDA's current thinking regarding information that industry should include in an ISE to provide an integrated analysis that offers insights beyond those observable in individual clinical trials.[3] This guidance does not apply to medical devices regulated as biologics under the Public Health Service Act.

This guidance supersedes section II.G., Integrated Summary of Effectiveness Data, of the guidance for industry *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* (Clin-Stat guidance).[4] It also incorporates the conceptual framework of section 2.7.3, Summary of Clinical Efficacy (SCE), from the ICH guidance for industry *M4E The CTD — Efficacy*.

[1] This guidance has been prepared by the Office of New Drugs and the Office of Biostatistics in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] See the Glossary for definitions and usage of specific terms used throughout this guidance.

[3] See 21 CFR 314.50(d)(5)(v). The ISE satisfies the regulatory requirement in 21 CFR 314.50(d)(5)(v) for drugs.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The ISE is a comprehensive integrated analysis of the effectiveness of a study drug. The purpose of the ISE is to describe the available information regarding effectiveness, delineate strengths and weaknesses, and highlight important missing information. Generally, analyses in the ISE are based primarily on the clinical effectiveness data included in the application, but they may also include other sources of information relevant to efficacy. Such sources include nonclinical studies; clinical pharmacology studies (e.g., pharmacokinetic (PK), pharmacodynamic, and in vitro studies) that describe dose-response, concentration-response, and drug-drug and drug-disease (e.g., renal dysfunction) interactions; human factor studies for drug-device combinations; and in vitro studies that clarify drug activity.

Since 1985, the regulation under 21 CFR 314.50(d)(5)(v) has required that the ISE be part of an NDA submission, but the regulation does not describe the specific components of the ISE in detail except for the components listed below. Under 21 CFR 314.50(d)(5)(v), the ISE must include:

- An integrated summary of the data demonstrating substantial evidence of effectiveness for each claimed indication
- Evidence that supports the dosage and administration section of the labeling, including support for the recommended dosage and dose interval
- Effectiveness data analyzed by sex, age, and racial subgroups, identifying any modifications of dosing 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

The first description of the purpose of an ISE was in the Clin-Stat guidance. Section II.G., Integrated Summary of Effectiveness Data, of that guidance stated:

> "The individual controlled studies to a great extent speak for themselves with respect to their ability to provide the evidence of effectiveness required by law. This section should provide an overview of the results, showing that they do satisfy the regulatory requirements for approval, i.e., represent adequate and well-controlled studies demonstrating the claimed effect, particularly if results are inconsistent or marginal. For example, the sponsor would explain here his basis for seeking to rely on a single study.

> Equally important, this section should include an examination of study-to-study differences in results, effects in subsets of the treated population, dose-response information from all sources, any available comparisons with alternative drugs, and any other information, so that the nature of the drug's effectiveness can be as fully defined as possible, and the user of the drug can be given the best possible information on how to use the drug and what results to expect."

The Agency interprets the regulation to refer not only to a discussion of the major effectiveness studies' results and design, but also to detailed integrated analyses of relevant sources of information concerning effectiveness. Such analyses generally fall into two broad categories: (1) comparing the individual studies to better understand the overall results (see section III.C.1., Comparison of Results of Individual Studies); and (2) using the greater power of pooled analyses to gain insight into the nature of the drug's effectiveness in demographic (e.g., age, sex, race, and ethnicity) and other subpopulations, into dose-response, and into onset and duration of effect (see section III.C.2., Pooled Analyses of Data From More Than One Study).

III. FORMAT AND CONTENT OF THE ISE[5]

The format (including section titles) of the ISE is flexible. In many cases (as described below) the ISE can closely follow the format of the SCE. Although applicants should take note of the following suggestions for content, they should choose the format that best suits the application. Applicants can consult with the appropriate review division to discuss specific plans for the ISE.

When critical to the understanding of study results, tables and figures from individual studies and pooled data should be embedded in the text (e.g., tables or figures showing results of important endpoint analyses). Lengthy tables, detailed endpoint assessments, and presentations of statistical approaches should be placed in an appendix, rather than the main body of the ISE. For the electronic common technical document (CTD), hyperlinks to tables should be provided within the body of the ISE.

When more than one ISE is provided for an application with more than one indication, each ISE should have its own appendix with tables.

The FDA is aware that there is a need for clarification regarding the scope and purpose of the ISE in relation to the content of the SCE. The ISE is a self-contained, detailed analysis that comprehensively examines relevant data from multiple sources intended to provide the substantial evidence of effectiveness for a given drug, and describes additional information related to that effectiveness, such as dose-response, effects in population subsets, or timing of response. The ISE should provide integrated analyses of the cumulative information that can help guide the effective use of a new drug. In contrast, the SCE is a compact summary of the critical findings reported in the ISE, including individual trial reports and the overall evidence of

[5] Some of the section headings in this guidance may be different from the section headings in 2.7.3, Summary of Clinical Efficacy. The headings in this guidance have been amended to correspond to the content within each section.

effectiveness. The SCE should not contain any information or data not discussed or explained in the ISE.

In some cases, the SCE can serve as the ISE if appropriate data can be included within the space limitations of the SCE. This approach can be feasible for relatively simple drug development programs such as those that rely on a single adequate, and well-controlled effectiveness trial, or a few trials of similar design. With respect to location of information within the CTD, the ISE should be included in Module 5, section 5.3.5.3, and the SCE in Module 2, section 2.7.3, as described in the guidance for industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.*

A. Listing and Brief Results of Individual Studies

A tabular listing of all studies relevant to drug effectiveness should be provided in this section. The tabulation and study descriptions will be used as an overview for subsequent analyses and comparisons of individual studies, as well as for analyses of pooled results. In addition to completed studies, the listing should include ongoing studies and those that were terminated (for such studies, there may be no results available). The listing should include studies reported both as integrated full reports and as abbreviated reports[6] as well as trials reported only as publications in the medical literature. Both positive studies and studies that failed to show effectiveness should be included.

The listing should be followed by concise descriptions of all completed well-controlled studies, whether or not they supported effectiveness. For each study, critical design features and important results should be briefly described, including the prospectively identified endpoints and planned statistical analyses. Similar studies can be described together, but the individual study results should be provided. These brief study descriptions should include references or electronic links to the full study reports. Each study presentation should provide enough detail to understand critical aspects of the study design and the study findings, including (as applicable) treatments compared, sample size, population studied, number and location of study sites, study drug dose and regimen, treatment duration, and results for primary and important secondary endpoints. In all cases, the observed results and estimates of effect (e.g., mean change from baseline on drug and placebo for blood pressure, progression-free survival for treatment and control arms in oncology studies, percent responders, hazard ratios), as well as confidence intervals and p-values should be provided.

[6] See the ICH guidance for industry *E3 Structure and Content of Clinical Study Reports*.

B. Analysis of Study Designs

This section should include discussion and critique of the important design features of all studies that sought to assess effectiveness, irrespective of whether the data support or do not support a conclusion of effectiveness. To the extent possible, the important design features and the statistical methodologies used to analyze the results of the controlled studies that were intended to support effectiveness should be presented for the studies as a group. Important similarities and differences among studies should also be presented (e.g., design, population, dose, duration, endpoints). Individual study reports should discuss these matters in greater detail.

Examples of these important design features are as follows (see ICH E3 for additional important study characteristics):

- Important inclusion and exclusion criteria that define the study population, for example:
  - Disease characteristics (e.g., severity, duration)
  - Demographic characteristics
  - Prior and concomitant illnesses
  - Treatment allowed, required, or not permitted
- Potential differences between the population(s) included in effectiveness studies and the overall patient population expected to receive the drug when it is marketed (e.g., exclusion of patients over 75 years old in studies of a drug for a disease common in the elderly).
- Type of control[7]
  - Placebo
  - No treatment
  - Active
  - Dose-response
  - Historical
- Specific treatments (e.g., dose, frequency) used in each group.
- Description of how concomitant treatment was chosen, if allowed for the disease or condition under study. For example, was it left to investigator choice? Were there any limitations? Were particular treatments required in both groups? Any differences in permitted concomitant therapies between treatment groups should be noted.
- Description of particular ancillary treatments (e.g., nonsteroidal anti-inflammatory drugs, proton pump inhibitors, drugs to manage hypertension) if required, encouraged, discouraged, or proscribed, and, where appropriate, the reasons for the treatments.

[7] See 21 CFR 314.126.

- Basis for choice of active control treatments, with particular attention to selection of the active control used in noninferiority designs, choice of noninferiority margin,[8] and support for the *constancy assumption* (i.e., the reason to believe that the effect of the active control drug in the present study is likely to have been similar to its effect in past studies).

- Choice of endpoints (primary and secondary), with particular attention to the validity of surrogate endpoints and novel clinical or patient assessments.

- Use of adjudication committees to assess endpoints.

- Study duration; treatment duration.

- Use of blinding, specific methods of blinding, and potential weaknesses (e.g., tablet enclosed in a capsule, odor of the study drug).

- Dosage selection and assessment of dose-response. Dose-response designs can include randomized fixed-dose dose-response, forced titration, and optional titration.[9] If the fixed-dose study had a titration phase or allowed upward or downward titration, this should be described.

- Randomization (e.g., stratified, nonstratified, allocation ratios).

- Use of enrichment approaches[10] to identify subjects with high likelihood of events (prognostic enrichment) or high likelihood of response (predictive enrichment), including randomized withdrawal design (a type of predictive enrichment). Any pharmacogenomic or proteomic assessments used in enrichment should be described.

- Use of other enrichment maneuvers (e.g., placebo run-in, means of encouraging compliance, exclusion of subjects with high baseline variability, use of less variable measurements, retention strategies).

- Adaptive features.[11]

- Use of a data monitoring committee and its specific responsibilities.

---

[8] See the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic.

[9] See the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration*.

[10] See the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic.

[11] See the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*. When final, this guidance will represent the FDA's current thinking on this topic.

- Planned endpoints, including primary endpoint(s) and secondary endpoint(s)
- Prespecified plans for statistical analyses, including:
  - Planned analysis for the primary efficacy endpoint
  - Planned sequential analyses
  - Analysis population (e.g., intent-to-treat, per protocol, as treated), with specific definitions
  - Methods for handling missing data
  - Methods of controlling type I error rate within studies when more than one endpoint or subpopulation is analyzed
  - Planned interim analyses
- Important changes in study design made after the start of the study, noting whether they were made before or after study unblinding
  - Change of primary endpoints during conduct of trial
  - Dropping or adding treatment arms
  - Changes in inclusion and/or exclusion criteria
  - Sample size modification
  - Planned adaptive features

C. Overall Analysis of Effectiveness Results

The term integrated analysis refers to using all relevant data from controlled trials, as well as other sources (e.g., clinical pharmacology trials), to enhance the understanding of the overall evidence of effectiveness. Integrated analyses include both close examination of individual study results and, when appropriate, combined quantitative analyses (pooled analyses). The integrated analysis is not a substitute for the analysis of individual studies. Instead, it is intended to provide a clearer understanding of responses across studies, different populations (e.g., demographic, disease-related), and dosing regimens. Differences in responses among studies should be described.

This section of the ISE should provide a comprehensive, integrated, in-depth analysis of the overall effectiveness results, with a rationale for the methods used in the analysis. All studies that sought to assess effectiveness should be included, irrespective of whether the data support, or do not support, a conclusion of effectiveness. The extent to which the results of the relevant studies reinforce or do not reinforce each other should be discussed.

The individual studies that are considered adequate and well-controlled investigations and that demonstrate the effect of the drug should be identified. These are studies that provide the

substantial evidence of effectiveness required for approval. Applicants should describe any aspects of study design and conduct that could call into question the adequacy of the studies, together with an explanation of why the studies should nonetheless be considered adequate and well-controlled.

The overall evidence of effectiveness should be examined, including assessments of study-to-study consistency with respect to, for example, subpopulation results, cumulative distribution of effects (i.e., not just mean effects), time of onset, and duration of effect.

The role of supportive data (such as data from animal models, pharmacologic effects, biomarkers, or studies of related diseases) should be described when appropriate, for example, when there is intent to rely on a single adequate and well-controlled clinical trial or where trials in different indications are intended to support approval for both conditions.

In general, applicants should seek to provide the following information in this section of the ISE:

- A discussion of what the collective evidence shows, including critical limitations.
- A discussion of all studies that were intended to support efficacy, including those that failed to achieve statistical significance on their efficacy endpoint(s), with an explanation of the observed differences in results, if possible.
- A discussion of incomplete studies, including: (1) studies terminated early because of lack of efficacy, a concerning safety signal(s), or other reasons; and (2) ongoing studies (e.g., long-term extension trials).
- The estimated effect sizes, confidence intervals, and p-values for the individual studies supporting effectiveness. A presentation of p-values alone would not be adequate.
- An assessment of the clinical meaningfulness of endpoints and their observed effect sizes.
- The consistencies and inconsistencies across studies, including subpopulation effects, dose-response.
- The reasons for considering some studies more persuasive than others.
- The problems arising from missing data and how these problems were addressed.
- The study features that posed particular analytic challenges (e.g., effectiveness scales, patient-reported outcomes, composite endpoints), when appropriate.

- In addition to effects on planned primary endpoints, an assessment, for studies that show an effect of time to onset of effect, and cumulative distribution of effects[12] (see section III.F., Time to Onset of Effect, Persistence of Effect and/or Tolerance, Distribution of Responses, for additional information).

As part of a comprehensive summary of experience related to effectiveness, this section of the ISE should include results of any other studies conducted using the study drug, published or unpublished, not conducted by the applicant, of which the applicant has become aware. Of particular interest are:

- Randomized, double-blind controlled clinical studies for the proposed indication
- Randomized, double-blind controlled clinical studies for a closely related indication
- Clinical studies exploring dose-response

In addition, this section of the ISE should include discussion of pertinent clinical pharmacology data (including population PK and concentration-response modeling data). Such data can clarify the exposure-response relationship, can contribute to a better description of dose-response, and can sometimes explain subpopulation differences. In addition to comparing estimates of exposure-response across trials, it is generally desirable to perform an exposure-response analysis on pooled data. Such an analysis may reveal relationships that would not be detected in a single study.

Particular attention should be paid to any recognized limitations of the effectiveness studies, such as short duration of study compared to specified use, small effect size, a number of failed studies of apparently adequate design, or reliance on a surrogate endpoint. Thus, if an effectiveness claim is based on a surrogate endpoint, the basis for choice of the endpoint should be discussed and its validity as a predictor of clinical outcome should be supported. This discussion may not be needed if the surrogate endpoint has been validated and relied upon as the basis of approval. For example, antihypertensive, oral hypoglycemic, and low density lipoprotein (LDL)-lowering drugs generally have been approved on the basis of demonstrated effects on blood pressure, blood sugar and HbA1c, and LDL cholesterol, respectively, without new evidence of an effect of the particular drug on survival or morbidity. However, any novel surrogate endpoint (i.e., one not used previously by the FDA as a basis for approval) should be discussed and supported.

As noted earlier, the analyses of effectiveness results generally should include two kinds of analyses: (1) comparison of results of individual studies; and (2) pooled analyses of data from more than one study.

1. Comparison of Results of Individual Studies

Results from all controlled studies should be summarized, examined, and compared, as appropriate, using tables and figures (such as forest plots). Important similarities and differences in patient populations (e.g., demographics, disease severity), control groups, doses, durations of

[12] See the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

exposure, inclusion or exclusion criteria, endpoints, and statistical methods should be identified. Applicants should describe differences in quality of blinding, dropout profiles, and variations in study conditions (such as differences in standard of care), as well as other factors they consider important.

Tables that show major study design features, number of subjects, number of dropouts, baseline values, and major outcomes can be of value.

Support for the proposed claim should be described in terms of the strength of statistical evidence, including consistency of findings, individual study strength, p-values, and confidence intervals. Findings that appear to weaken or limit the claim (e.g., failed or negative studies, including studies stopped for futility at an interim analysis) are important and should be described as well.

Comparisons of results across studies should focus on the prespecified primary endpoints. However, when important data elements are common to all studies (even if not the primary endpoint), analyses of such elements can provide an important assessment of consistency. For example, in a series of studies where an important variable was assessed at multiple time points, an analysis comparing results obtained at a common time point should be shown, even if the time point for the primary analysis differed among studies. For studies employing composite endpoints, where there are clinically important events that occur infrequently (e.g., death), a comparison of frequencies or rates of this event across studies should be displayed. If results as a function of time are important, study results can be displayed in a figure that illustrates the change over time in each study, again, even if this was not a primary endpoint. Important secondary endpoints, particularly in the context of a study that succeeded in achieving the primary endpoint, should also be shown.

Ordinarily, studies with similar controls (e.g., placebo control, active control) should be discussed together. Graphic displays of common analyses can be helpful. Forest plots can be used to display study results on a common axis. These plots can show individual study p-values and confidence intervals.

If there are important differences in outcome among studies of generally similar design, these differences should be displayed and discussed. Factors such as differences in subject demographics, disease definition, disease stage, disease severity, prior treatment, drug dose or regimen, or methods of observation may underlie such differences. Unanticipated study conditions (e.g., site-related differences in standard of care) that could explain differences in effectiveness should be identified where possible. Often such analyses will raise questions for future exploration rather than provide definitive answers.

2. Pooled Analyses of Data From More Than One Study

Analyses that use information combined from all studies also should be performed as part of the ISE. In contrast to the overview of individual studies, which compares and contrasts outcomes from individual studies, these analyses should be performed by pooling subject-level data or pooling common outcomes from individual studies. There is no consensus on how best to perform pooled analyses, and a variety of methods can be used. The applicant should explain the

specific analyses used and the reasons for their selection. Formal meta-analysis procedures that produce valid effect estimates and associated uncertainties should be used when appropriate.

Data should be pooled to examine the effect of demographic (e.g., age, sex, race, and ethnicity) and other characteristics (e.g., presence of specific concomitant illnesses or treatments), where the individual studies would have too few subjects with these characteristics to support meaningful conclusions. These subpopulation analyses are discussed in section III.D., Comparison of Results in Subpopulations. Pooled analyses can be performed on study-level summary data or on subject-level data.

Differences among individual studies can affect the validity and interpretability of pooled analyses. Particular caution is warranted when the studies differ with respect to:

- Important demographic or disease characteristics (e.g., duration, severity, specific signs and symptoms, previous treatment, concomitant diseases and treatments, prognostic or predictive biomarkers)

- Treatment practices, including methods of assessing effectiveness, specific test procedures (e.g., methods of exercise testing, pulmonary function testing)

- Study design features (e.g., study duration, study size, doses studied, allocation ratio to treatment and control arms, visit frequency)

Such differences can make study results heterogeneous, requiring cautious interpretation. Thus, consistency of populations and treatment practices across studies should be examined before pooling. When significant heterogeneity is not observed, pooling can reveal subpopulation differences that could not be detected in individual studies. Differing allocation ratios across studies need to be taken into account in pooling (Dong 2005).

Although there are occasional clinical development programs that include a planned analysis of efficacy across more than one study, such analyses are unusual. For example, an NDA could include two large cardiovascular outcome studies, each examining major adverse cardiovascular events as their primary endpoint (e.g., cardiovascular death, nonfatal heart attack, and nonfatal stroke). A prospectively planned analysis of mortality across both studies can be specified as part of the development plan. Because prospectively planned efficacy analyses across two or more studies in a development program is uncommon, the majority of pooled analyses described for inclusion in the ISE are exploratory in nature. They are designed to probe the data for trends across more than one study (e.g., in disease-specific subgroups, trends across multiple doses).

D. Comparison of Results in Subpopulations

Subpopulation assessments, required under 21 CFR 314.50(d)(5)(v), can identify differences in the effectiveness profile of the drug among subpopulations. Such differences, if found, may be important. Subgroup analyses should be viewed as a component of the overall assessment of safety and efficacy but generally should not be intended to support statistically meaningful interpretations of the data in a particular subgroup. To that end, an integrated analysis of the

effect of treatment in subpopulations of interest should summarize and compare results across the controlled studies that are described in the ISE, both in individual studies, where there is sufficient subgroup representation, and in pooled analyses. Although all controlled trials should be pooled for these analyses, applicants also should provide a separate analysis that excludes studies in which no overall treatment effect was demonstrable.

Subpopulations analyzed should include those defined by major demographic factors (e.g., age, sex, and race or ethnicity), as required by 21 CFR 314.50(d)(5)(v), and those that can be analyzed by other predefined or relevant intrinsic and extrinsic factors (e.g., disease severity, prior treatment, concomitant illness, concomitant drugs, alcohol or tobacco use, body weight, renal or hepatic function), or by region. For continuous variables (e.g., age, weight, creatinine clearance), subgroup analyses by quartile or quintile should be considered, in addition to analyses using fixed cut-points (e.g., age older than 75).

The integrated analysis should examine the consistency of the observed treatment effect across individual studies for demographic subpopulations and for other relevant subpopulations. For example, if effectiveness data are generated from trials both within and outside the United States, there should be comparisons of results in U.S. and non-U.S. populations. The assessment across subpopulations can highlight apparent variations in effectiveness that call for further investigation and discussion. However, the limitations of such analyses should be recognized.[13] It is important to note that their purpose is not to provide the basis for specific claims or to attempt to improve the evidence of effectiveness in situations where the individual study results are disappointing.

As noted, the integrated subpopulation analyses should include both individual studies (where subpopulations are large enough for this to be useful) and pooled analyses. For the larger subpopulations (e.g., sex subgroups), there should be a side-by-side summary and comparison of individual study results. For ease of visual comparison, results could be presented as forest plots and as tabular summaries showing point estimates and confidence intervals. Forest plots can be used to display subset results in large outcome trials and meta-analyses of trials to assess dichotomous cardiovascular endpoints, (i.e., event: yes/no). They also could be used to show subset analyses of pooled data from trials designed to ameliorate the symptoms of a disease or condition.

In most cases, analyses of subpopulation effects in data pooled across studies are more likely than analyses in individual studies to have adequate power to assess differences. A quantitative analysis of data pooled across studies generally should be shown. Consideration should be given to conducting analyses that both include and omit studies that failed to show an effect. Differences among subpopulations that are consistent across studies and of a meaningful size from a clinical perspective may generate hypotheses that can be tested in future studies. In some cases, where results are persuasive, it is important to describe differences in effects in subpopulations.

[13] See the ICH guidance for industry *E9 Statistical Principles for Clinical Trials*.

E. Analysis of Clinical Information Relevant to Dosing Recommendations

This section should provide an integrated summary and analysis of all data, including data from individual dose-response clinical studies, relevant pooled analyses, and clinical pharmacological studies, that pertain to the dose-response or blood level-response relationships of effectiveness (including dose-blood level relationships). These data contribute importantly to dosing recommendations, including the choice of dose interval. The individual study results and any cross-study analyses that will be used to support the dosing recommendations (including the recommended starting and maximal doses, the method of dose titration, dose schedule, and any other instructions regarding individualization of dosage) should be summarized here. These results and analyses should include descriptions of relatively straightforward dose-response or blood level-response relationships as well as any identified deviations caused by nonlinearity of pharmacokinetics, delayed effects, tolerance, or enzyme induction. Limitations of the data (e.g., titration designs were used instead of fixed-dose designs) should be described and assessed.

Differences in PK or pharmacodynamic responses should be discussed, or discussions can be cross-referenced in section 2.7.2, Summary of Clinical Pharmacology Studies, CTD Module 2. Differences in dose-response relationships that result from age, sex, race, ethnicity, disease, or other factors should also be described. The methods for evaluating differences should be described, even if no differences were found. Examples include specific studies in subpopulations, analyses of effectiveness results by subpopulation, and blood level determinations of the study drug.

F. Time Course of Effect, Persistence of Effect and/or Tolerance, Distribution of Responses

For both symptomatic treatments and drugs that affect outcome (e.g., cardiovascular outcome studies, oncology studies), the time course of the effect should be displayed. These can usually best be displayed graphically (e.g., difference in symptom scores between drug and placebo over time; Kaplan-Meier curves for cardiovascular outcome studies and oncology studies).[14]

Therapeutic effects of a treatment can decline over time because of tolerability issues (subjects who experience adverse events and refuse treatment), or from the development of drug resistance or tolerance (loss of therapeutic effects over time), or because the disease tends to resolve spontaneously. Applicants should provide the number of subjects for whom long-term effectiveness data are available; the dose, duration of exposure, and the reason for discontinuation.

The focus of the analysis of persistence of effectiveness and/or tolerance effects analyses should be controlled studies specifically designed to collect effectiveness data. For example, a randomized withdrawal study is a powerful method of assessing persistence of effect. The controlled studies should be clearly differentiated from other, less rigorous studies, such as open-

[14] See the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

label extension studies. Data relevant to withdrawal or rebound effects should be presented in the appropriate safety sections.

In addition to mean drug effect in a study, the distribution of responses in individuals should be examined and displayed. Distributions can be displayed using histograms to show outcomes or changes of various sizes for treatment and control groups (e.g., the number or percentage of subjects with worsening symptoms or change in effectiveness measure, and 0 to 10 percent, more than 10 to 20 percent, more than 20 to 30 percent, etc., improvement in symptoms or change in effectiveness measure) or by using cumulative distribution curves, showing the effect in all subjects in treatment and control groups.

G. Exploratory Investigations

Results of exploratory analyses based on endpoints, patient subpopulations, and pooled data not specified in the protocol can be reported. Such analyses may provide important insights, or lead to hypotheses for examination in future studies.

GLOSSARY

Drug — For purposes of this guidance, this term refers to both human drugs and biological drug products regulated by the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research unless otherwise specified.

Efficacy and Effectiveness — These terms are used variably and often interchangeably by the scientific and regulatory communities. For purposes of this guidance, the term *effectiveness* is being used because it is the more commonly cited term in the Code of Federal Regulations, and is defined for purposes of this guidance as referring to the therapeutic effect (i.e., effect on signs, symptoms, or outcomes of a disease or condition) of the drug.

Integrated Analysis — For purposes of this guidance, this term refers to using the collective results of individual studies to provide further insight into the effectiveness of a study drug.

Pooled Analyses — This term has sometimes been referred to broadly as meta-analyses but many observers have distinguished between the two terms based on the methodological rigor needed for valid meta-analyses. Nevertheless, for purposes of this guidance, this term refers to all analyses of data from more than one study.

Subgroups, Subpopulations, and Subsets — For purposes of this guidance, these terms are used interchangeably.

REFERENCES

Literary

Dong, J, 2005, Simpson's Paradox, Encyclopedia of Biostatistics, Online, John Wiley & Sons, Ltd., http://onlinelibrary.wiley.com/doi/10.1002/0470011815.b2a10055/compoundindex.

EMEA, 2000, Committee for Proprietary Medicinal Products (CPMP) Points to Consider on Validity and Interpretation of Meta-Analyses, and One Pivotal Study (***DRAFT***), EMEA, EWP secretariat, October, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003659.pdf.

National Research Council, 2010, The Prevention and Treatment of Missing Data in Clinical Trials, Washington, DC: The National Academies Press.

Guidances and MAPPs[15]

Draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*[16]

Draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*[17]

Draft guidance for industry *Non-Inferiority Clinical Trials*[18]

Guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*

Guidance for industry *Guideline on Format and Content of Clinical and Statistical Sections of an Application*

Guidance for industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*

[15] Guidances for industry can be found on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. MAPPs can be found on the Manual of Policies and Procedures Web page at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

[16] When final, this guidance will represent the FDA's current thinking on this topic.

[17] When final, this guidance will represent the FDA's current thinking on this topic.

[18] When final, this guidance will represent the FDA's current thinking on this topic.

Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*

Guidance for industry *Providing Regulatory Submissions in Electronic Format — Standardized Study Data*

ICH guidance for industry *E3 Structure and Content of Clinical Study Reports*

ICH guidance for industry *E5 Ethnic Factors in the Acceptability of Foreign Clinical Data*

ICH guidance for industry *E9 Statistical Principles for Clinical Trials*

ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials*

ICH guidance for industry *M4E The CTD — Efficacy*, Section 2.7.3, Summary of Clinical Efficacy

MAPP 6010.3 Rev.1 *Clinical Review Template*, Attachment A, Section 6, Review of Efficacy

MAPP 6010.4 *Good Review Practice: Statistical Review Template*