# Guidance for Industry

## E9 Statistical Principles for Clinical Trials

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)
September 1998
ICH

# Guidance for Industry

## E9 Statistical Principles for Clinical Trials

*Additional copies are available from:*

*Office of Training and Communications*
*Division of Drug Information (HFD-240)*
*Center for Drug Evaluation and Research (CDER),*
*5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573*
*http://www.fda.gov/cder/guidance/index.htm*

*or*

*Office of Communication, Training, and Manufacturers Assistance (HFM-40)*
*Center for Biologics Evaluation and Research (CBER)*
*1401 Rockville Pike, Rockville, MD 20852-1448*
*http://www.fda.gov/cber/guidelines.htm; (Fax) 888-CBERFAX or 301-827-3844*
*(Voice Information) 800-835-4709 or 301-827-1800*

**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)**
**September 1998**
**ICH**

# TABLE OF CONTENTS

# GUIDANCE FOR INDUSTRY[1]

## E9 Statistical Principles for Clinical Trials



## I. INTRODUCTION

### A. Background and Purpose (1.1) [2]

The efficacy and safety of medicinal products should be demonstrated by clinical trials that follow the guidance in *E6 Good Clinical Practice: Consolidated Guidance* adopted by the ICH, May 1, 1996. The role of statistics in clinical trial design and analysis is acknowledged as essential in that ICH guidance. The proliferation of statistical research in the area of clinical trials coupled with the critical role of clinical research in the drug approval process and health care in general necessitate a succinct document on statistical issues related to clinical trials. This guidance is written primarily to attempt to harmonize the principles of statistical methodology applied to clinical trials for marketing applications submitted in Europe, Japan and the United States.

As a starting point, this guidance utilized the CPMP (Committee for Proprietary Medicinal Products) Note for Guidance entitled *Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorizations for Medicinal Products* (December 1994). It was also influenced by *Guidelines on the Statistical Analysis of Clinical Studies* (March 1992) from the Japanese Ministry of Health and Welfare and the U.S. Food and Drug Administration document entitled *Guideline for the Format and Content of the Clinical*

[1] This guidance was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, February 1998. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States. This guidance was published in the *Federal Register* on September 16, 1998 (63 FR 49583), and is applicable to drug and biological products.

[2] Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, February 1998.

*and Statistical Sections of a New Drug Application* (July 1988). Some topics related to statistical principles and methodology are also embedded within other ICH guidances, particularly those listed below. The specific guidance that contains related text will be identified in various sections of this document.

*E1A* *The Extent of Population Exposure to Assess Clinical Safety (March 1995)*
*E2A* *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (March 1995)*
*E2B* *Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (January 1998)*
*E2C* *Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (November 1996)*
*E3* *Structure and Content of Clinical Study Reports (July 1996)*
*E4* *Dose-Response Information to Support Drug Registration (November 1994)*
*E5* *Ethnic Factors in the Acceptability of Foreign Clinical Data (June 1998)*
*E6* *Good Clinical Practice: Consolidated Guideline (April 1996)*
*E7* *Studies in Support of Special Populations: Geriatrics (August 1994)*
*E8* *General Considerations for Clinical Trials (December 1997*
*E10* *Choice of Control Group in Clinical Trials (September 1999)*
*M1* *Standardization of Medical Terminology for Regulatory Purposes (November 1999)*
*M3* *Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (July 1997)*

This guidance is intended to give direction to sponsors in the design, conduct, analysis, and evaluation of clinical trials of an investigational product in the context of its overall clinical development. The document will also assist scientific experts charged with preparing application summaries or assessing evidence of efficacy and safety, principally from clinical trials in later phases of development.

## B. Scope and Direction (1.2)

The focus of this guidance is on statistical principles. It does not address the use of specific statistical procedures or methods. Specific procedural steps to ensure that principles are implemented properly are the responsibility of the sponsor. Integration of data across clinical trials is discussed, but is not a primary focus of this guidance. Selected principles and procedures related to data management or clinical trial monitoring activities are covered in other ICH guidances and are not addressed here.

This guidance should be of interest to individuals from a broad range of scientific disciplines. However, it is assumed that the actual responsibility for all statistical work associated with clinical trials will lie with an appropriately qualified and experienced statistician, as indicated in ICH E6. The role and responsibility of the trial statistician (see Glossary), in collaboration with other clinical trial professionals, is to ensure that statistical principles are applied appropriately in clinical trials supporting drug

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.