
Good Review Practice: Clinical Review of Investigational New Drug Applications

This document has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

December 2013

Table of Contents

1.	INTRODUCTION	1
2.	GENERAL CONSIDERATIONS	2
2.1	Pre-IND Meeting/IND Original Submission	2
2.2	Phase 1 Clinical Trial Protocol	4
2.3	End-of-Phase 2/Phase 3 Planning	5
2.4	Controlled Clinical Trial Protocol Review (including Special Protocol Assessments)	8
2.5	Fast Track or Breakthrough Designation	11
2.6	IND Safety Reports (21 CFR 312.32(c))	12
3.	DOSING AND CLINICAL PHARMACOLOGY.....	13
3.1	Phase 1 Tolerability Trials	13
3.1.1	Choosing a Starting Dose for Phase 1	13
3.1.2	Dose-Escalation and Maximum Dose and Duration in Phase 1 ...	15
3.1.3	Toxicity-Induced Modifications in Enrollment or Dosing (Safety Rules)	17
3.2	Pharmacokinetic and Pharmacodynamic Trials.....	17
3.2.1	Effect of Intrinsic and Extrinsic Factors on PK and PD	18
3.2.2	Classic PK Clinical Trials (Frequent Sampling).....	19
3.2.3	Population PK Clinical Trials	19
3.2.4	Bioavailability and Bioequivalence Trials.....	19
3.2.5	Drug-Drug Interactions	20
3.3	Choice of Dosing Interval.....	21
4.	ASSESSING DOSE-RESPONSE.....	22
4.1	Fixed-Dose Clinical Trials	24
4.2	Titration Clinical Trials.....	25
4.3	Crossover Dose-Response Trials	26
5.	CONTROLS, TRUTH STANDARDS, AND COMPLIANCE	26
5.1	Types of Controls.....	26
5.1.1	Placebo Control.....	27
5.1.2	No-Treatment Control.....	28
5.1.3	Dose-Comparison Control	28
5.1.4	Active-Treatment Control.....	29
5.1.5	External (Historical) Control	31
5.2	Trial Design Features.....	32
5.2.1	Randomized Withdrawal Trials	32
5.2.2	Adaptive Designs	33
5.2.3	Enrichment.....	33
5.2.4	Crossover and Multiple Treatment Trials	34
5.2.5	Trials in Nonresponders or Intolerants	34
5.3	Truth Standards.....	34
5.4	Assessing Treatment Compliance.....	35
5.5	Background Care and Standard of Care.....	35
6.	RANDOMIZATION AND BLINDING.....	36

6.1	Randomization	36
6.1.1	Fixed-Randomization Schemes	37
6.1.1.1	Blocked randomization	37
6.1.1.2	Stratified randomization	38
6.1.2	Adaptive-Randomization Schemes.....	39
6.1.3	Allocation Ratio	39
6.1.4	Review of Randomization.....	40
6.2	Blinding.....	40
6.2.1	Optimizing and Maintaining the Blinding.....	41
6.2.1.1	Character of the placebo and trial drug	41
6.2.1.2	Unblinding drug effects	41
6.2.1.3	Dealing with imperfect blinding	42
6.2.1.4	Assessing unblinding	42
6.2.1.5	Blinded evaluators or evaluation committees.....	42
7.	PATIENT POPULATIONS, SPECIAL POPULATIONS.....	43
7.1	Trial Population	43
7.1.1	Homogeneity vs. Heterogeneity; Individualization of Treatment	44
7.1.2	Factors Influencing the Nature of the Trial Population	44
7.2	Special Populations, Demographic Subgroups.....	45
7.2.1	Subgroup Analyses vs. Special Population Trials	46
7.2.2	Pediatric Populations	46
7.2.2.1	Timing of studies in pediatric populations	49
7.2.2.2	Types of studies in pediatric populations	51
7.2.3	Women.....	52
7.2.3.1	PK issues regarding women	53
7.2.3.2	Interactions with oral contraceptives	53
7.2.3.3	Studying pregnant women	54
7.2.4	Elderly Subjects	54
7.2.5	Racial Groups.....	55
7.2.6	Other Subpopulations of Interest: Genetic, Proteomic, and Concomitant Illness	56
7.3	Patient Population Size	57
7.3.1	Sample Size in Phase 1 Clinical Trials	57
7.3.2	Sample Size in Phase 2 and Phase 3 Clinical Trials	57
7.3.3	Total Population Exposure.....	59
8.	STATISTICAL ANALYSIS PLANS	60
8.1	Planned Analyses	60
8.1.1	Adequacy of the Statistical Analysis Plan	61
8.1.2	Reviewing Changes to the Statistical Analysis Plan.....	63
8.1.3	Interim Analysis Plans	64
8.1.3.1	Confidentiality of interim data	64
8.1.3.2	Stopping rules for an early finding of efficacy or toxicity	65
8.1.3.3	Risks of early stopping for efficacy	66
8.1.3.4	Unplanned interim analyses	66
8.1.3.5	Reviewer's role during the trial	67

8.1.4	Intent-to-Treat Analysis	67
8.2	Endpoints	68
8.2.1	Primary Endpoints	69
8.2.1.1	Composite endpoints	72
8.2.2	Secondary Endpoints	73
8.2.2.1	Descriptive analyses	74
8.2.3	Surrogate Endpoints.....	74
8.2.4	Patient-Reported Outcome Measures	76
8.3	Discussions With the Sponsor	77
8.3.1	Target Product Profile.....	77
8.3.2	Continuous Involvement.....	77
9.	GOOD CLINICAL PRACTICES	78
9.1	The Institutional Review Board.....	79
9.2	Informed Consent.....	80
9.2.1	Consent in Pediatric or Other Vulnerable Populations.....	81
9.2.2	Waiver of Informed Consent	82
9.3	Investigator’s Brochure.....	82
9.4	Investigator Qualifications and Responsibilities	83
9.5	Trial Monitoring and Auditing.....	83
10.	ADVERSE DRUG EXPERIENCES AND REPORTS.....	84
10.1	Safety Monitoring	84
10.2	Reporting Requirements for Sponsors	86
10.3	IND Safety Reports — Written Reports	87
10.3.1	Definition: Adverse Event	88
10.3.2	Definition: Adverse Reaction	88
10.3.3	Definition: Suspected Adverse Reaction	89
10.3.4	Definition: Unexpected.....	89
10.3.5	Definition: Serious.....	89
10.3.6	Definition: Life-Threatening.....	90
10.4	Assessment of Adverse Drug Reports	90
10.5	Actions After Reviewing Adverse Drug Reports	91
10.6	Annual Reports	92
10.7	Other Safety Data.....	93
11.	EXPEDITED DRUG DEVELOPMENT PROGRAMS	93
11.1	Serious or Life-Threatening Condition.....	94
11.2	Available Therapy.....	95
11.3	Demonstrating the Potential to Address Unmet Medical Need	96
11.4	Qualifying Criteria for Expedited Drug Development Designations.....	97
11.4.1	Fast Track	97
11.4.2	Breakthrough Therapy	98
11.5	Features of Expedited Drug Development Designations....	100
11.5.1	Features of Fast Track.....	100
11.5.2	Features of Breakthrough.....	100
12.	REFERENCES	101

13. GLOSSARY OF ACRONYMS107

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.