
CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

*The FDA published Good Guidance Practices in February 1997.
This guidance was developed and issued prior to that date.*

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) <http://www.fda.gov/cder/guidance/index.htm>

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

Guideline for the Clinical Evaluation of Analgesic Drugs

Revised December 1992

This publication may be reproduced without permission of the
Food and Drug Administration

Comments on the contents of this publication are invited and
should be addressed to the following office,
and identified with the docket number:

Docket Number 91D-0425
Dockets Management Branch (HFA-305)
Room 1-23
12420 Parklawn Dr.
Rockville, Maryland 20857

For further information regarding the guideline, please contact:

Group for Analgesic Drugs
Pilot Drug Evaluation Staff (HFD-007)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

TABLE OF CONTENTS

	<u>Page</u>
ABSTRACT	iii
FOREWORD	iv
I. INTRODUCTION	1
II. PRECLINICAL STUDIES	1
III. CLINICAL STUDIES	1
A. Phase 1	1
1. Initial Phase 1 Studies	1
2. Repeated-dose Phase 1 Studies	2
3. Late Phase 1 Studies	2
B. Phase 2	3
1. Investigators	3
2. Patient Population	3
3. Laboratory Studies Relating to Safety	4
4. Selection of Appropriate Treatments and Controls	4
i. Placebo and standard drug controls	5
ii. Relative potency assays	6
iii. Other study designs used in early dose ranging	6
iv. Choice of doses of the test drug	7
v. Choice of analgesic standards	7
5. Allocation of Patients to Treatments (parallel-group and crossover designs; randomization)	7
6. Number of Patients in the Study	8
7. Measures of Analgesic Effect	9
i. Indices of Pain Relief and Pain Intensity	9
ii. Onset of Analgesia	10
iii. Duration of Analgesia	10
iv. Qualitative Effects	10
v. Total Effects (Area Under the Time-Effect Curves)	10
vi. Quantal Effects	11
vii. Alternative Measures of Analgesia	11
8. Alternative Approaches to the Demonstration of Analgesic Efficacy	12
9. Use of the Double-Blind Technique	12
10. Concomitant Medication	12
11. Side Effect Information	13
12. Studies in Particular Patient Populations	13
i. Postoperative pain	13
ii. Postpartum pain	14

- iii. Chronic pain 14
- iv. Dysmenorrhea 14
- v. Headache 14
- vi. Outpatient studies 15
- vii. Experimentally induced pain 15
- 13. Pharmacokinetics and Pharmacodynamic Studies of
 Analgesics and Pharmacokinetics as a Basis for
 Choosing Different Doses 16
- 14. Evaluation of Analgesics with Different Time
 Courses of Action 17
- 15. Analgesic Drug Combinations 18
- 16. Analgesic Combinations of an NSAID with a Narcotic
 Analgesic 19
 - i. General considerations 19
 - ii. Single-Dose Clinical Studies 19
 - iii. Multiple-Dose Clinical Studies 21
- C. Phase 3** 21
 - 1. Patient Population--Types of Pain to be Studied 22
 - 2. Multidose, Short-Term Therapy 22
 - 3. Chronic Administration 23
 - i. Peripherally Acting or NSAID Oral Analgesics 24
 - ii. Centrally Acting Oral Analgesics 24
 - iii. Oral Combination Analgesics 24
 - 4. Children and Women of Childbearing Potential 24
- D. Special Studies** 25
 - 1. Drug Dependence Liability 25
 - 2. Side Effect Liability 25
- IV. LABELING CONSIDERATIONS** 26

ABSTRACT

The Food and Drug Administration (FDA), with the assistance of consultants, Advisory Committees, and specialty subcommittees of professional societies, such as the American Society of Clinical Pharmacology and Therapeutics, has developed guidelines for the clinical evaluation of new drugs. This is one in a series of clinical guidelines that present recommended current approaches to the study of investigational drugs in humans, and pertain to Phases 1 through 3 of the investigation. They represent generally accepted principles for arriving at valid conclusions concerning safety and effectiveness of new drugs, as well as the views of experts concerning appropriate methods of study of specific classes of drugs.

FDA welcomes comments on the guidelines, and expects to keep them current by review and update.

FOREWORD

The purpose of this guideline is to present recommended current approaches to the study of investigational drugs in humans. This guideline contains both generalities and specifics, and was developed from experience with available drugs. The design of clinical studies, in compliance with the recommendations in this guideline, does not imply that data obtained in such studies will necessarily result in the approval of an application, or that the studies suggested will produce the total clinical information required for approval of a particular drug. It is anticipated that, with the passage of time, this guideline will require revision.

A person may choose to use alternate procedures even though they are not provided for in the guideline. If a person chooses to depart from the practices and procedures set forth in the guideline, that person may wish to discuss the matter further with the agency to prevent an expenditure of money and effort on activities that may later be determined to be unacceptable by FDA. This guideline does not bind the agency, and it does not create or confer any rights, privileges, or benefits for or on any person.

Many of the clinical guidelines have been developed largely, or entirely, by FDA's Advisory Committees and consultants. Others were originally developed by intramural committees and consultants of FDA, the Pharmaceutical Manufacturers Association, or, as in this case, by a subcommittee of a professional association with expertise in the field of analgesia; in all these cases, the guidelines were reviewed and revised, as appropriate, by FDA's staff and Advisory Committees.

GUIDELINE FOR THE CLINICAL EVALUATION OF ANALGESIC DRUGS

I. INTRODUCTION

"General Considerations for the Clinical Evaluation of Drugs" is an important companion piece and should be reviewed before reading these guidelines. It contains suggestions that are applicable to investigational drug studies for most classes of drugs and enables elimination of repetitious material in each of the specific guidelines. In addition, principles set forth for "adequate and well-controlled clinical investigations" (21 CFR 314.126(b)) are applicable to the clinical evaluation of analgesic drugs.

II. PRECLINICAL STUDIES

In addition to those studies routinely done to define the general pharmacologic profile of a new agent, animal trials should be performed to determine the category of analgesics into which the test compound falls. A useful current categorization is (1) those analgesics that are narcotic-like, (2) those which have associated narcotic antagonist properties, (3) those "peripherally acting" drugs that have associated anti-inflammatory and/or antipyretic effects such as aspirin, and (4) those which do not seem to fall into any of the other groups. This categorization is of importance in choosing suitable prototypes to be used as standards of comparison in subsequent clinical studies and in identifying the type of adverse effects for which clinical investigators must be particularly vigilant.

An already marketed nonsteroidal anti-inflammatory drug (NSAID), when combined with an already marketed narcotic agent, should be tested through (1) the standard preclinical studies for the NSAID and (2) teratology studies of the combination in two species.

III. CLINICAL STUDIES

A. Phase 1

1. Initial Phase 1 Studies

Although either normal adult volunteers or patients with pain are acceptable subjects, initial Phase 1 studies of analgesics are preferably performed in normal, institutionalized adults.

Studies should be performed with the subjects in a closely supervised setting to explore for side effects or evidence of organ toxicity when the new agent is administered over a dosage range and for a duration of administration that is appropriate for the proposed Phase 2 studies to

explore effectiveness. Phase 1 studies involving multiple daily doses of the drug administered for more than a few days are neither necessary nor desirable until properly controlled Phase 2 studies have demonstrated that single doses of the drug have useful analgesic activity in humans. (See Section III. A. 2. Repeated-Dose Phase 1 Studies.) A concurrent placebo treated control group should be used and is particularly helpful in assessing the significance of subjective side effects. For some Phase 1 studies, a positive control may be appropriate to assess the sensitivity of the assay for certain special toxicologic properties, e.g., aspirin in fecal blood loss studies.

A complete physical and extensive laboratory examinations should be performed before and at intervals during the study. Effects on vital signs and organ function should be monitored during the study.

Narcotic agonists and antagonists should be scrutinized for bizarre psychic effects.

Provisions should be made, when technically feasible, to determine absorption (e.g., blood level and urinary excretion curves following single doses). It is of particular importance to establish the extent and rate of oral absorption in a dose range predicted on the basis of animal studies to have biological activity.

Metabolism, distribution, and plasma-binding experiments should be undertaken as soon as technically feasible, but need not delay testing for therapeutic effect.

The routes of administration in Phase 1 studies should encompass all of those intended for use in Phase 2.

2. Repeated-Dose Phase 1 Studies

After properly controlled Phase 2 studies have established the efficacy and usual analgesic dose of a new non-narcotic oral analgesic, and before the drug is administered to patients on a chronic basis in Phase 3 studies, normal adult volunteers should receive repeated doses of the drug for 1 to 2 weeks (at least five times the half-life of the drug or its active metabolite with the longest half-life). The dosage regimen should be at least equal to the highest total daily dose contemplated in patients, and, if not precluded by adverse effects, the effect of higher dose levels should also be investigated. Complete physical and extensive laboratory examinations should be performed at intervals during and at the completion of the study.

3. Late Phase 1 Studies

Very often, certain Phase 1 studies are performed late in the clinical development of an analgesic. This happens, in particular, when the pharmacokinetics of a drug are investigated in specific subpopulations of prospective patients: in subjects of different age groups or of different sex, in individuals with impaired kidney or liver functions, in volunteers who are overweight or underweight, etc. Though these trials occur late in the development of the drug, they are still considered Phase 1 studies; the findings from these late Phase 1 studies are of paramount

significance for the proper use of the analgesic drug and are, therefore, an important part of the labeling of the drug.

B. Phase 2

The principles governing the methodology, analysis, and interpretation of controlled clinical trials of analgesic efficacy are discussed in detail in the scientific literature. Because methodology does, and should, change with continuing growth of knowledge about analgesics and analgesia, sponsors of INDs should follow the literature, scientific conferences, analgesic drug approvals, and FDA Advisory Committee meetings.

Initial Phase 2 analgesic studies usually examine the effect of single doses of a drug across a range of doses. The purpose is to determine what dose or doses to take into later Phase 2 trials, where substantial evidence of the drug's analgesic effect is established. A common mistake, which can cause substantial delay in bringing a drug to market, is a poor choice of the dose(s) to take into later Phase 2 and Phase 3 trials. The initial Phase 2 studies should explore a wide enough range of doses and pain models to provide a solid foundation for the narrower range of doses taken into later Phase 2 studies.

Multiple-dose studies should produce information about how the test drug compares with standard analgesics in terms of onset of analgesia, peak analgesia, and duration of analgesia, as well as side effects in the clinical setting where the drug is most likely to be used. This is important in introducing new analgesics to physicians, because usual clinical trial efficacy-outcome variables are less easily translated into directions for use than are direct comparisons with standard analgesics (see Section IV. LABELING CONSIDERATIONS).

1. Investigators

Early Phase 2 investigators should be experienced in the design and conduct of trials of analgesic drugs.

2. Patient Population

In early Phase 2 studies, patients should usually be institutionalized or at least be under the surveillance of the investigator during the anticipated course of action of the drug. (For exceptions, see pages 7 and 8 of "General Considerations for the Clinical Evaluation of Drugs.")

The type of patient or "pain model" selected for the study will depend on preliminary judgments whether the agent involved is a strong or a mild analgesic and whether initial studies are to be conducted using the parenteral or oral route. Since the discriminatory ability of subjects has often proven better when analgesics have been administered parenterally, there may be an advantage in terms of assay sensitivity in using subcutaneous or intramuscular administration in initial studies.

Analgesics are usually assayed in models such as postoperative pain, including oral surgery and cesarean section, cancer pain, postpartum pain (episiotomy pain or uterine cramps), sore throat pain, headache, mixed pain, which includes acute trauma and various types of musculoskeletal pain. Levels of pain intensity vary widely within each of these pain models, and thus there is no absolute specificity of pain model for either strong or mild agents. However, models do differ in their sensitivity to detect differences between weak or strong analgesics (see Section III. B. 4. Selection of Appropriate Treatments and Controls).

Several models may be used for both parenteral studies and oral studies. The specific pain model should be selected on the basis of the known assay sensitivity of the model and on the appropriateness of that model for the analgesic chosen as the standard (see Section III. B. 4); the standard analgesic usually tells more about pain control in a given pain model than the patient's pain perception (moderate, severe, etc.).

The use of patients with pain of mixed etiology is not recommended in Phase 2 studies, as it invariably decreases assay sensitivity and potentially leads to results that are difficult to interpret unless suitable stratification procedures are employed. For example, in an assay comparing analgesics with and without anti-inflammatory activity in a sample of patients with pain of mixed etiology, an unequal distribution of patients with pain and those with pain associated with inflammatory disease among treatment groups may confound interpretation of the effectiveness of an analgesic that possesses also anti-inflammatory activity. Furthermore, recent studies indicate that accepted general pain models that do not involve patients with inflammatory disease may be more sensitive to narcotic agents as opposed to NSAID analgesics. Careful consideration should, therefore, be given to this point in the choice of pain models and positive control treatments in the evaluation of a new analgesic.

To provide "substantial evidence" for the efficacy of a new analgesic, several different pain models should be represented among the successful controlled trials of analgesic efficacy. It is desirable to explore the use of the test drug in as many models as possible. Replicate evidence of efficacy should be obtained in at least two of these models. More than one study site should be used to replicate the results. To assess the evidence fully, all available studies will be considered.

At least some of the studies should be performed in the United States to increase the likelihood that patient-population-related differences in efficacy and side effect liability could be recognized.

3. Laboratory Studies Relating to Safety

In Phase 1, extensive laboratory studies (e.g., hematologic, hepatic, and renal) as well as appropriate special laboratory tests should be performed at intervals and 24 hours after the last dose in patients receiving the test medication on a chronic basis. Unless there are particular safety concerns arising from the results of Phase 1 studies, laboratory studies need not be

routinely performed in Phase 2 analgesic studies that entail the administration of only a single dose or a few doses of test drug.

4. Selection of Appropriate Treatments and Controls

Although Phase 2 may be initiated with single-blind, uncontrolled dose-ranging studies of the test drug, the sooner double-blind studies using an appropriate standard of comparison can be initiated, the better. The study design should include a comparison of one or more dose levels of the test drug with a placebo and, generally, with a standard analgesic.

i. Placebo and standard drug controls

The efficacy of a particular dose level of the test drug may be established by demonstrating a statistically significant difference in analgesic effect in a simple comparison with a placebo. Although a positive result in such a comparison is of some value, a negative result (i.e., no difference demonstrated between the test drug and the placebo) may indicate that the dose of the test drug was inappropriately chosen, that the sample size was too small, or that the assay method used was not sufficiently sensitive to detect an analgesic effect. Likewise, a comparison of the test drug with a standard analgesic only, each at a single-dose level, may yield useful information if the test drug proves to be significantly superior or inferior to the control drug; but a finding of similar performance for both drugs may again merely be an indictment of the sensitivity of the assay and does not establish the efficacy of the test drug. At least partial insurance against these ambiguous outcomes may be achieved by the incorporation into the study of both a placebo and a standard analgesic in addition to the test drug. This design provides an internal measure of the sensitivity of the assay (i.e., the method should be able to distinguish the placebo from the standard), and, in addition, a measure of the performance of the test drug in comparison with a commonly used analgesic. To explore the dose-response curve of the test drug, this design is usually extended to include, in addition to a placebo and a single-dose level of the standard, two or more dose levels of the test drug. When two doses of a standard or test drug are used, it is important, from the pharmacodynamic standpoint, that they be at least twofold different and that the drug's variability in pharmacokinetics be such that there is little projected overlap in peak levels or amount of drug absorbed.

In addition to graded doses of the test analgesic, more than one standard analgesic may be incorporated in the study design. Usually, one of the standards (high standard) is chosen on the assumption that it is more effective than the other (low standard), and the demonstration of a significant difference between the two serves as a measure of "upside" assay sensitivity in the study. The ability to demonstrate a significant difference between low standard and placebo validates the "downside" assay sensitivity of the study. Generally, pain models do not have wide enough sensitivity to optimally deal with both "downside" and "upside" sensitivity, i.e., to show a dose-response of a mild (needs

"downside" sensitivity) and a strong (needs "upside" sensitivity) analgesic in the same study.

Regardless of the control treatments chosen, it is necessary to incorporate some method of verifying assay sensitivity into every study performed, even though exactly the same methodology is ostensibly being used in each; the demonstration that one study was able to discriminate between treatments does not prove that another study, even in the same pain model, will have a similar outcome. A study that does not contain some measure of assay sensitivity generally does not provide substantial evidence for the efficacy of a test analgesic.

ii. Relative potency assays

A special case of using standard drugs as controls, particularly useful where placebo treatment is not possible or not practical, is the estimation of the relative potency of the test drug in relation to a standard analgesic. This may be obtained by an assay, or a series of assays, employing graded doses of both the test and standard medications. When planning a relative potency assay, it is advisable to consider the following: (1) The dose-response curves of the standard and test drugs are more likely to be parallel if the standard chosen is in the same pharmacologic class as the test drug, and (2) both drugs should have similar onset, peak effect, and duration of analgesia, and any difference in effect should only be dose-dependent. There are some differences of opinion about the utility of the relative potency assay when the time-effect curves of the two drugs (test and standard drug) being compared are dissimilar; in such cases, it would be wise to consult FDA as well as outside experts about the applicability of this test to the particular situation. Because this methodology is intended to establish equi-effective doses of the test drug and the standard, it facilitates a subsequent meaningful determination of the relative side-effect liability of the two drugs. In addition, the demonstration of a significant common dose-response regression for the standard and the test drug serves as an alternative to using differences between a placebo and a standard as a measure of assay sensitivity, thus eliminating the necessity of incorporating a placebo in the study design. The statistical treatment and interpretation of the data generated by a clinical analgesic relative potency assay is similar, in most respects, to those appropriate for relative potency bioassays.

iii. Other study designs used in early dose ranging

A series of studies may be done involving paired comparisons of a single-dose level of the standard with increasing single doses of the test drug. The effect of the test drug can also be explored by the demonstration of a statistically significant, positive, dose-response regression for the test drug, but this design has the disadvantages of not establishing the efficacy of the lowest dose of test drug administered, unless a placebo-

treatment group is included, and it does not provide any comparison with a standard analgesic.

iv. Choice of doses of the test drug

Regardless of the design of Phase 2 studies, these trials, taken together, should explore the entire dose-response curve of the test drug and should be the basis for selecting the dose used in later Phase 2 and Phase 3 studies. In addition, some data should be collected on doses above and below the recommended dose. It is advisable, whenever technically feasible, to obtain blood level data on patients in analgesic trials to further stratify analgesic response. Establishing such a relationship may allow more precise dosing, and may lead, ultimately, to dosing recommendations based on patient characteristics, e.g., body weight, ideal body weight, renal function, etc.

v. Choice of analgesic standards

The choice of the active control(s) should be appropriate for each pain model utilized. When possible, most of the Phase 2 studies should compare a test drug with analgesic standards that have a similar mechanism of action; NSAIDs are best compared with NSAIDs and opioids with opioids. The choice of active controls is also relevant in facilitating appropriate analgesic labeling (see Section IV. LABELING CONSIDERATIONS).

Morphine is the most widely used standard of comparison for strong injectable analgesics and aspirin and ibuprofen for nonsteroidal anti-inflammatory analgesics. Acetaminophen and codeine are also often used as standards for (weaker) oral analgesics. Combinations of aspirin or acetaminophen with codeine or oxycodone may be useful as standards in studies of oral analgesics that are more effective than aspirin or acetaminophen, but the use of a drug combination as the sole standard in a study intended to provide substantial evidence of efficacy is not recommended because of problems in interpreting the results.

A combined oral-parenteral study using a double-dummy technique and an injectable analgesic as a standard may be useful when evaluating oral analgesics with efficacy in the range of strong parenteral analgesics.

5. Allocation of Patients to Treatments (parallel-group and crossover designs; randomization)

In the clinical evaluation of analgesic efficacy, investigators have used two basic designs in comparing treatments. Patients may be assigned to one of two or more treatment groups, the patients in each group receiving only a single treatment administered once or repeatedly (parallel-group study design). Alternatively, each patient may be used as his/her own control by giving him/her sequentially more than one treatment (the crossover design). Both complete

and incomplete block crossover designs have been used in analgesic assays; in either, the sequence of treatments in the crossover should be balanced for order. In all cases, the design of the study must provide for the random allocation of patients to treatments, or treatment sequences.

The salient advantage of crossover designs lies in the potential for reduction of experimental intersubject variation, which may arise, in parallel-group designs, from the unequal distribution between treatment groups of known and unknown patient variables capable of influencing treatment outcome. Crossover designs also make maximal use of those patients who could productively evaluate more than one dose of study medication. The major disadvantage of crossover designs is that certain features of the resulting data may considerably complicate the interpretation of the trial results. These complicating features are:

- i. Interaction among treatments in the study, which may take the form of pharmacologic or psychologic carryover effects.
- ii. Trend effects in the underlying source of the pain that tends to increase or decrease during the time-interval of patient participation.
- iii. Dropouts leading to loss of data. If the dropouts are unequally distributed among treatment sequences, bias may be introduced. However, if properly designed, a crossover study may be analyzed using the first-dose-only analysis (as a parallel study) in addition to the analysis based on patients who complete the crossover.

The parallel-group design, while free of carryover effects among study treatments, is not free of the pharmacologic and/or psychologic carryover effects from the routine analgesics which subjects for analgesic studies take if they have chronic recurring pain. Crossover design allows for at least some evaluation of interactions and carryover effects; parallel-group design does not. The parallel-group method may be more influenced by variability among patients than the crossover method and requires a relatively large or homogeneous patient population. The effect of between-patient variation in a parallel-group study may be reduced by stratification of the patient sample on the basis of initial severity. As a rule, crossover analgesic studies require patients with recurring pain of the same intensity before each treatment arm.

Whether crossover or parallel-group design will yield the most efficient assay in any particular investigational setting, where the use of either is feasible, can only be settled empirically.

6. Number of Patients in the Study

The number of patients necessary to produce an acceptable level of assay sensitivity in an analgesic study depends on the variance, the magnitude of difference to be detected, and the desired power. Different investigators and different pain models do not necessarily require the same number of patients per treatment group to demonstrate statistically significant differences.

Likewise, because of the additional sources of variation, multi-investigator studies **generally** require a larger total number of patients per treatment group to achieve the same power as that obtained at a single study site. To obtain an estimate of the sample size necessary to show a specific difference requires a statistical power calculation. Such calculations are **based** on specific assumptions and statistical models. These should be carefully considered with respect to their likely validity and the implications of the clinical significance of the differences or similarities to be detected.

Most published parallel studies use from 30 to 50 patients per treatment group. Under certain circumstances, sequential analysis, using appropriate statistical procedures, has also been used for determining the size of the patient sample during a study.

7. Measures of Analgesic Effect

i. Indices of Pain Relief and Pain Intensity

Analgesic effectiveness has been scored by a number of rating systems that are explained in the analgesic literature, and most investigators employ multiple rating systems in each study. The most successful systems have been those that have accepted the patient's own reports as appropriate indices of pain severity and pain relief resulting from analgesic administration.

Typically, full-time, trained observers, under the investigator's supervision, are used to obtain informed consent from patients and to monitor the study. Inpatient studies require trained personnel to ascertain when patients have the correct level of pain to enter a study. In such studies, the trained observer generally administers the study medication and then interviews the patient at appropriate intervals. Outpatient studies usually rely on patients making their own assessments on a take-home diary. Trained personnel, under the investigator's supervision, are necessary to select patients for the study and to give the appropriate instructions for taking study medication and filling in the diary.

The interview points and total duration of observation for a study are adapted to the anticipated time-effect characteristics of the agent under test and may vary from 4 to 12 or more hours.

The development program for an analgesic should collect data to describe adequately onset of effect, peak effect, and duration of effect. There are many ways to collect data on these measures of efficacy. Some early studies should have blood level measurements taken at the time of pain assessment.

ii. Onset of Analgesia

Measurement of onset of action should be included in analgesic studies. At present, the methods for doing this are varied with no one method being generally accepted. Recently, several investigators have applied survival analysis techniques to determine onset. Examples of the different methodologies include: (1) The use of a stopwatch by the patient to measure the time after dosing when the patient first detects or notices pain relief, (2) asking the patient to retrospectively estimate when relief first occurred, and (3) pain relief and pain intensity at specific time points when a specified interval change is attained in an efficacy parameter, such as pain relief or pain intensity. In terms of mean responses to treatment, onset may be taken as the observation point at which the treatment becomes significantly superior to placebo.

iii. Duration of Analgesia

Similar to onset of analgesia, there are various approaches to defining the duration of analgesia. Examples include: (1) The time from administration of study medication, or onset of analgesia, until the intensity of pain returns to baseline, or the patient indicates that analgetic effect is vanishing; (2) the time from administration of study medication, or onset of analgesia, until the patient requests remedication; (3) the time-interval when half of the patients did remedicate; and (4) the percentage of patients who did not remedicate at any time-point.

iv. Qualitative Effects

The patient's and/or investigator's global evaluation of the study medication constitutes another index of analgesic efficacy. However, it should not be considered alone since it contains no information concerning time-effect characteristics of the treatments. The global evaluation may be on a graded scale, e.g., poor, fair, good, very good, or excellent, or simply a categorization scale of, e.g., "success" or "failure."

Methods for rating the affective or sensory qualitative features of pain or concomitant mood states may provide useful, supplementary evidence that may help characterize the effects produced by single-ingredient or combination analgesic drugs.

v. Total Effects (Area Under the Time-Effect Curves)

The possible range of pain intensity or pain relief is often distributed over a 4-point scale such as "pain relief" ratings of none (0), a little (1), some (2), a lot (3), or maximum (4). These scores are weighted according to the time intervals of the interview points and the (weighted) scores are summed across the observation period to generate an estimate of the area under the curve. Peak effects for pain intensity, pain intensity difference, and pain relief can be generated from these data.

vi. Quantal Effects

Although quantal measures of effect potentially provide lower assay sensitivity, they can produce useful support data. Examples of quantal measures are whether or not the patient has experienced "50%-relief" or whether relief was "satisfactory or unsatisfactory" at each interview point.

vii. Alternative Measures of Analgesia

As an alternative or in conjunction with verbal rating scales, Visual Analog Scales are also acceptable as measures of analgesic effect.

Secondary assessments that have been used successfully in the evaluation of analgesics include objective measurements on vital capacity and peak expiratory flow rate following upper abdominal surgery.

Various measures of analgesia that can be derived from the above scoring systems include:

- (1) Changes in pain intensity (pain intensity differences) are calculated from the patients' estimates of the intensity of their pain by subtracting the pain level at each observation point after medication from the intensity at the time of administration;
- (2) "Total" or summary effect scores that estimate the area under the analgesic time-effect curve for each treatment can be derived by summing the scores across observation points for each of the measures of analgesic effect (i.e., pain severity or pain intensity, change in pain intensity or pain intensity difference, pain relief, and 50%-relief); or
- (3) The time-to-remedication can be used as a measure of analgesia if the criteria for remedication are appropriate and uniform (see above). The percentage of patients, either remaining or dropping out of the study at each observation point, also can be used as a measure of analgesia. Estimates of the comparative efficacy, such as onset and duration of analgesia, etc., will probably differ to some degree, particularly when comparing treatments with different time-effect curves. No conclusions can be drawn regarding relative potency when time-effect curves differ (see Section III. B. 4. Relative Potency Assays).

The arbitrary dichotomization of an array of graded data derived from one of the above scoring systems into "success" or "failure" categories after completion of a study risks the introduction of bias unless the criteria for such dichotomization are specified prior to the accumulation of the data.

Although analgesic scores represent ordinal rather than interval data, experience has shown that these scores are sufficiently similar to interval data to allow the use of usual parametric statistical procedures in their analysis. Alternatively, rank or other transformations may be employed as well as other nonparametric statistical approaches, and a few studies have successfully used sequential statistical techniques. In each case it is necessary to examine how the data are distributed and whether or not they fit the necessary assumptions required by the method of analysis.

8. Alternative Approaches to the Demonstration of Analgesic Efficacy

Although the above noted pain models, study designs, and methods of measuring analgesic effect encompass those used in the majority of published controlled clinical analgesic studies, other approaches may provide equally valid evidence of analgesic efficacy. The development of useful new techniques is desirable. Novel approaches to study design and analgesic scales may be validated by demonstrating that they have the requisite assay sensitivity to distinguish known effective standard analgesics from placebo or from each other or that they can demonstrate an analgesic dose response curve.

9. Use of the Double-Blind Technique

Because of the subjective nature of the pain experience and the potent effect of expectation on the patient and the observer, the double-blind technique must be employed in controlled trials of analgesics. This may best be achieved by the individual coding of each treatment for each patient.

10. Concomitant Medication

During the conduct of Phase 2 analgesic trials, concomitant psychoactive medication should be discontinued, if possible, or kept at a constant, previously established, minimal dose. Other analgesics should not be given during the period when the effect of the study medication is being evaluated unless dosing with concomitant medication is used as a measure of efficacy. However, it must be realized and accepted that very few eligible candidates for analgesic studies are naive subjects in the sense that they have not had previous experience with analgesic or anesthetic medications. In the case of patients with chronic pain, it is seldom either practical or ethically acceptable to demand an extended washout period before the administration of a study medication. Most investigators require that a patient's pain return to baseline (i.e., no relief left) and at least 2 to 3 hours have elapsed since administration of the previous analgesic dose. Likewise, some provision must be made to limit the length-of-time that a patient, who receives an ineffective study medication, is asked to wait before being allowed to re-medicate.

11. Side Effect Information

Phase 2 controlled analgesic studies involving the administration of single doses are not designed primarily for the evaluation of drug side effects, and side effect information must be considered as secondary to the data on analgesic effectiveness. Observers should record at least apparent and volunteered side effects, and reports of side effects are often elicited by a nonleading question such as: "Is there anything else that bothers you?" or "Did you notice any other effects from the medication?" Patients are usually not questioned in detail concerning a specific list of side effects, nor are laboratory tests performed in the short-term analgesic studies except in unusual circumstances.

Because the minor subjective side effects most often associated with analgesic administration (e.g., sedation, dizziness, nausea, dyspepsia, sweating, headache, etc.) are also common concomitants of the patient's disease (e.g., cancer with associated chemotherapy or radiotherapy) or the postoperative or postanesthetic state, it is usually impossible for the investigator to estimate the likelihood of a causal relationship between such symptoms and the treatment administered to any particular patient. However, in larger studies in which there is a dose-related occurrence or more frequently observed side effects, it is possible to make a reasonable estimate of the relative side effect liability of the treatments. In addition, certain side effects are sufficiently unusual (e.g., a florid psychotomimetic reaction to a narcotic antagonist) to leave little doubt in the investigator's mind as to the causal connection with the treatment.

It is usual to observe differences among studies in the incidence of side effects associated with particular treatments. Most of these differences probably result from differences in the subject samples (etiology and severity of pain, extent of ambulation, prior or concomitant medication, socioeconomic and ethnic background), methods of eliciting side effect reports, and observer-patient interaction.

12. Studies in Particular Patient Populations

i. Postoperative pain

Patients with postoperative pain have been used successfully to assay both strong and mild analgesics. Moderate to severe pain following opening of the major body cavities, other general and special surgical procedures, surgery on the skeletal system, and tooth extraction have been used. Patients with mild pain, such as after episiotomy, have been found to discriminate less well between active drug and placebo. While both crossover and parallel-group experimental designs have been used, experience has shown that the pain following the less traumatic surgical procedures is often of such short duration that the large number of patients who do not re-medicate are a problem in crossover studies.

ii. Postpartum pain

Patients with postpartum pain can be used in the evaluation of mild analgesics. The possibility of drug excretion in breast milk may suggest the exclusion of nursing mothers. If patients with postpartum uterine cramping are used in the same study with patients with postepisiotomy pain, the study sample should be stratified for these two types of pain. Study designs using parallel treatment groups have usually been found superior to crossover design in postpartum studies.

iii. Chronic pain

Patients with chronic pain, usually due to cancer or associated with chronic musculoskeletal and peripheral vascular disease, may be used to assay both strong and mild analgesics. The general characteristics of the study are in most respects similar to those for acute pain, except that the crossover approach is frequently used to take advantage of the chronicity of the pain. Each treatment in the crossover may be given once or administered repeatedly, and the crossover may or may not be replicated.

Chronic pain is necessary to evaluate the development of tolerance, cross-tolerance, or cumulative effects. If it is not possible to discontinue the administration of other drugs for one or two weeks before the trial, prior use of such drugs may influence the results of the study to the extent that they influence the absorption, metabolism, or excretion of the study medications. Physical or psychological dependence or tolerance to a prior drug may also influence the evaluation.

iv. Dysmenorrhea

Primary dysmenorrhea is a good pain model for repeat-dosing of NSAIDs because of their prostaglandin synthesis inhibitory effect. The antiprostaglandin potency of an NSAID is thought to be directly proportional to the analgesic efficacy in this model. Besides a placebo control, the active control should be chosen on the basis of proven analgesic effectiveness in dysmenorrhea. Because of less variability between the recurrent pain in the same individual than between different individuals, primary dysmenorrhea is also a good model for crossover studies. The data derived from two menstrual cycles for each treatment are more powerful than those from only one cycle, but require different statistical analyses than studies using one cycle.

v. Headache

Headache is a symptom reported in conditions of diverse etiology. Several classes of drugs (analgesics, muscle relaxants, tranquilizers, vasoconstrictors, ergot preparations)

may have drug class-specific beneficial effects on various subclasses of the total headache population. When choosing headache as a pain model, it is therefore essential to consider these varied etiologies in the selection of patients for study. Some types of headache, in the same way as dysmenorrhea, are suitable pain models for crossover studies because of the recurrent nature of the painful episodes.

vi. Outpatient studies

Although the hospital environment itself is quite variable, in general it is subject to much more control than can be exerted over an outpatient population. In the latter situation, observations are often made at less frequent intervals and may require substantial retrospection on the part of the patient. The situation offers no guarantee that the patients will not take interfering medications or that they will take the test medications as prescribed or fill out their diaries at the prescribed time. Considerable ingenuity is necessary in the design and execution of outpatient studies to circumvent these difficulties. However, several recent studies in outpatients with pain due to surgical removal of impacted third molars, dysmenorrhea, and tension headache have demonstrated that it is indeed possible to do outpatient studies of oral analgesics and analgesic combinations that demonstrate a level of assay sensitivity comparable to that obtained in good inpatient studies.

The common features of these successful outpatient studies have been careful screening of patients to identify subjects capable of understanding the requirements of the study and motivated to follow the protocol; systematic, detailed instruction of these patients to maximize compliance with the requirements of the protocol; use of carefully designed and validated patient report forms on which the patients recorded their pain intensity and analgesic response at intervals during the time-course of the study medication and/or close telephone contact with the patients; and meticulous followup to minimize dropouts.

In some studies, oral surgery outpatients or women with dysmenorrhea have volunteered to remain in the investigator's facility for a sufficient period of time after surgery to allow supervised administration of study medication and recording of observations at intervals comparable to those used in inpatient studies.

vii. Experimentally induced pain

Early attempts to use experimentally induced pain in humans for the assay of analgesic drugs yielded inconsistent results that often correlated poorly with the performance of analgesics in pain due to injury or disease. These discrepancies were in part due to the use of pain generated by acute cutaneous stimuli as the predominant measure of analgesic effect. More recent studies, which have focused on changes in the tolerance of subjects to more severe and protracted experimental pain rather than alterations in cutaneous pain

threshold by drugs, have produced results more consistent with the results of analgesic studies in the pathologic pain models discussed above. Evidence is still inadequate to establish that any experimental pain model will consistently and accurately predict the clinical efficacy of new analgesics; although studies using experimental pain may be useful in early Phase 2 trials, they cannot substitute for controlled trials in patients with pathologic pain in producing substantial evidence of analgesia and establishing proper directions for use in the labeling of the drug. However, studies of analgesics in experimentally induced pain may constitute a useful screening technique and may complement the results of clinical trials by elucidating mechanisms of analgesic action and other pharmacologic issues that do not lend themselves to be studied in clinical use pain models.

13. Pharmacokinetics and Pharmacodynamic Studies of Analgesics and Pharmacokinetics as a Basis for Choosing Different Doses

Pharmacokinetics quantitatively describes the time course of drug disposition in the body. Drug disposition includes the rates and extent of drug entry (including intravenous infusion and oral or intramuscular absorption), distribution, biotransformation, and elimination. Pharmacodynamics defines the relationships between biofluid drug concentrations (usually blood or plasma) and intensity of therapeutic and toxic pharmacological effects.

Standard pharmacokinetic parameters include mean estimates and their range for: systemic clearance, elimination half-life, volumes of distribution, rate and extent of bioavailability, blood (or plasma) protein binding fraction excreted unchanged in urine, and metabolic profile. Pharmacokinetic studies should be designed to assess intra- and interindividual variation as well as the dose-linearity of clearance, and to generate reliable pharmacokinetic parameters in the dose range of pharmacodynamic interest. Biofluid sample collection should be of sufficient frequency and duration to provide a complete concentration-time profile as anticipated from the time-effect curve for the analgesic by the intended route or mode of administration.

Pharmacokinetic data should be collected in appropriate patients as well as from normal subjects. The patient studies provide the opportunity to concurrently collect pharmacokinetic and pharmacodynamic data including measures of pain intensity and pain relief. This information on pharmacokinetic-pharmacodynamic relationships can provide a knowledge base that may be useful for establishing the optimal dose range and choosing dosing regimens for chronic administration. Although the relationship between blood concentration-time profiles and analgesic time effect curves is complicated and may require the use of pharmacokinetic-pharmacodynamic models and/or population pharmacokinetic methods, investigators are encouraged to collect and analyze these data intensively in Phases 1 and 2, and sparingly in Phase 3 studies.

At present, while two formulations of a particular analgesic may be assumed to provide equivalent analgesia if they produce congruent curves of active drug in the blood, controlled clinical trials are necessary to demonstrate the clinical relevance of any significant difference observed in the blood concentration-time profiles produced by different formulations of an analgesic unless pharmacokinetic-pharmacodynamic data are available to provide an estimate of the consequences, if any, of this variation.

The available information on the routes of elimination and pathways of biotransformation will dictate additional pharmacokinetic studies, which may include measurement of biofluid concentrations of parent and active metabolites in special risk patient populations. These populations generally include the elderly and patients with renal and/or hepatic dysfunction.

Pharmacokinetic studies should be included in the design of chronic administration studies with the objective of estimating the rate and extent of accumulation of parent drug and its metabolites, under apparent steady-state dosing conditions. Pharmacokinetic (e.g., one or a few biofluid samples) data, comparing responders with dropouts, sustained responders, or those with unexpected toxic effects, can provide valuable information on the sources of variation in analgesic response observed during chronic studies.

14. Evaluation of Analgesics with Different Time Courses of Action

Special issues arise when evaluating a drug with a different course of analgesic effect compared to a specified reference drug. The test drug could be a new drug or a different formulation of a marketed drug. Issues that need to be addressed include time-to-onset, peak effect, time-to-peak, and duration of effect. Pharmacokinetic and pharmacodynamic data are critical in deciding specific study designs to relate differences in the time course of blood levels to clinical (beneficial and adverse) effects.

Comparisons of SPID (Sum of Pain Intensity Differences) and TOTPAR (Total Area Under the Pain Relief curve) measurements for active drugs with different time-effect curves are generally not useful for overall comparisons of effectiveness. If multiple doses of a shorter acting control are used, SPID and TOTPAR may be compared for time periods of the shorter acting drug. With comparisons of this type, onset and duration of effect may not be discriminating measures of therapeutic effect, although a rough overall comparison might be made. In each case, the intervals for following patients and/or redosing should be geared to accommodate both drugs and not bias one or the other through arbitrarily selected time intervals for comparison.

Hourly pain and relief measurements may be useful within each study design. Time-to-event measurements become important, including (i) time to peak relief, (ii) time to onset, (iii) time-to-redosing, and (iv) length-of-time from onset to redosing (duration). With these time-to-event measures, survival time methods of analysis may be appropriate.

15. Analgesic Drug Combinations

FDA's general policy regarding fixed-combination prescription drugs codified in 21 CFR 300.50(a) applies to analgesic drug combinations.

The claims proposed for a particular combination are critical in determining the kinds of clinical trials that are appropriate for its evaluation. Acceptable claims for the combination must be specified and the clinical studies, to verify these claims, must be designed to substantiate them. Studies of a combination may require different methods, depending on the putative advantages to be claimed.

To provide substantial efficacy information, single-dose studies must be performed in which the combination is compared to the individual components, to a placebo, and to standards that adequately delineate both "downside" and "upside" assay sensitivity of the model, depending on the circumstances.

The contribution of each of two analgesics to the effect of their combination is usually best studied using a factorial experimental design. This may be a simple 2x2 factorial experiment (placebo, single doses of each of the two analgesics, and the combination) or may consist of more complicated designs (including graded doses of either one or both analgesics alone and, possibly, graded doses of the combination). Statistical tests of the hypothesis concerning the superiority of the combination to each component should be performed.

A factorial design for studying combinations of analgesics with other classes of drugs, e.g., mood-altering drugs, muscle relaxants, etc., may also be appropriate to demonstrate that the combination produces more beneficial effects than either drug alone.

In situations in which one of the components has been documented to have little or no analgesic effect, the full factorial design may not be necessary and the less effective treatment can be substituted for the placebo to validate the assessment of analgesic effect. In this situation, the more effective constituent needs to be significantly superior to the less effective or ineffective constituent. The proof of greater effectiveness of the combination would then depend on pairwise treatment contrasts of the combination with the more effective component.

In the case of prescription combinations of an analgesic with a drug intended for a concomitant but unrelated indication (e.g., pain relief and sleep enhancement, pain relief and decongestion, pain relief and muscle relaxation, etc.), or new OTC combinations not covered by monographs, studies should be performed in appropriate models to investigate the effects of the combination in patients having both target conditions to show that both drugs in the combination contribute to the claimed effect.

As with any analgesic agent (single entity or combination), the development program needs to determine dose-effect, onset of effect, peak effect, duration of effect, and overall performance

of the drug (see section on Measures of Analgesic Effect; Multi-dose, Short-term Therapy; and Phase 3, pages 9, 22, and 21, respectively).

In the case of new OTC combinations of single agents, for which the OTC combination of similar agents is covered by monographs, it may only be necessary to identify the segment of the consumer population that needs both drugs for optimal relief of multiple symptoms. Phase 3 studies may still be necessary to assess the recommended dosing schedule (see Phase 3 section, page 21).

16. Analgesic Combinations of an NSAID with a Narcotic Analgesic

i. General considerations

FDA's general policy regarding fixed combination drugs, as described above, is applicable to analgesic combinations of an NSAID with a narcotic agent as well.

Clinical requirements for a marketed NSAID, combined with a narcotic analgesic, include (1) biopharmaceutical studies to define the rate and extent of absorption for each component of the combination with 90% power to show a 20% change in either rate or extent of absorption, (2) single-dose safety/efficacy studies, and (3) multiple-dose safety/efficacy studies.

The requirements for approval of a combination vary, depending on the intended claim, e.g., (1) the combination might enhance the speed of onset of pain relief of a drug with a long half-life, (2) the combination might achieve satisfactory efficacy in painful conditions not adequately provided by either agent by itself, or (3) an oral combination might prolong the duration of analgesia.

In preliminary studies, a sponsor may experiment with several pain models to determine the one best suited to demonstrate the intended benefit of the combination.

In patients with pain so severe that placebo treatment is not feasible, assay sensitivity is ordinarily assessed by using more than one dose of an effective agent. In the case of NSAID/narcotic combinations, inclusion of the NSAID alone and NSAID/narcotic-groups is recommended to provide the means to judge assay sensitivity.

ii. Single-Dose Clinical Studies

Development of a fixed combination of an NSAID with a narcotic agent for painful conditions requires evidence of efficacy in two pain models. Since the analgesic efficacy of the NSAID and the narcotic agent will have been previously established, FDA requires either two studies in a single pain model, or one study in two pain models, that demonstrate the superiority of the

combination to each of its components. This assumes that, in studies not showing efficacy, the explanation for the failures is reasonably apparent from the control groups.

Test drugs are typically studied in a 2x2 factorial design, in which the combination must be shown to be superior to each component, and the NSAID must be superior to placebo. Note that it is not generally possible or necessary to demonstrate the superiority of a single dose of an oral narcotic to placebo. However, a study in which the combination was superior to its components, but the effectiveness of the NSAID over placebo or the oral narcotic was not seen, might provide some supportive data, but such a peculiar result would weaken the overall evidence of effectiveness.

For painful conditions, in which a placebo control group is not feasible, by just comparing the combination with each of its components, the combination must be shown to be superior to the NSAID or narcotic alone in a study that provides assurance of adequate assay sensitivity.

In order to provide labeling information for the patient population for whom the combination is appropriate, the test combination should be compared to a suitable positive control. This should be a standard treatment not only approved for use in the patient population but one that has significant general acceptance and use. In order to validate the performance of the positive control in the chosen pain model, it must be distinguishable from the least effective control, i.e., generally the treatment with placebo or an oral narcotic.

A finding of "no difference" between treatments establishes their comparability in the treatment of pain that is characteristic for the pain model used, if each is significantly better than the least effective control.

The two requirements (1) demonstrating that each component contributes to the claimed effects, and (2) establishing the appropriateness of labeling claims for treating pain usually medicated with standard narcotic-containing combinations or more potent analgesics can be fulfilled in the same study or in separate complementary studies. These studies should include an assessment of the effects of the drug on the central nervous system (i.e., mood changes, drowsiness, etc.) as well as classic pain assessment.

In order to make claims of comparability of particular doses of drugs with different pharmacokinetic and pharmacologic profiles over time, it is necessary that the time-effect curves show comparability at all time points during the treatment interval. If the shape of the time-effect curves are different, e.g., if one drug peaks earlier but its effects have dissipated by 4 hours (common with narcotics) whereas the other drug peaks slower but lasts 6 to 12 hours (common with some NSAIDs), potency comparisons based on SPIDs and TOTPARs are not valid, and comparability statements may not be appropriate at all.

iii. Multiple-Dose Clinical Studies

In FDA's experience, single-dose studies underestimate the incidence of adverse effects that will be seen in ordinary use of the drugs, which usually involves multiple doses. Similarly, adverse effects seen in trials of patients who require analgesics less than 2 weeks may not adequately reflect the incidence of adverse effects in patients who need pain medication more chronically. The following clinical investigations are late Phase 2 studies, or trials performed in Phase 3.

(a) To demonstrate efficacy in patients with usual short-term use and to accumulate safety data adequate to define whether the frequency of adverse effects associated with usual usage at the 1 to 3% level is grossly different from alternative treatments (i.e., more than a fivefold increase), there should be controlled studies, extending 2 or more days, involving multiple doses and measuring both safety and efficacy. These studies should be controlled by using a currently marketed standard drug appropriate for the patient population, and should involve at least 100 patients on combination and at least an equal number of control patients. It is recognized that pain assessment in such studies is not as rigorous, as a rule, as in the single-dose trials.

(b) In addition, to define whether the adverse effects associated with chronic usage are grossly different from those observed with alternative treatments (see above), there should be controlled studies of 1 to 3 months duration of daily dosing, measuring safety and efficacy, and using as a control a currently marketed standard drug appropriate for the patient population. These studies should involve patient groups of the same size as above, i.e., 100 patients per treatment group.

C. Phase 3

Phase 3 trials are intended to assess the effectiveness of the recommended dosage schedule under conditions of use and to assess safety sufficiently to predict the usual side effects that will be encountered in broad clinical use. In Phase 3, several issues need to be addressed. These include the interaction of the drug with a variety of disease states and therapeutic regimens, as well as a judgment as to the "clinical acceptability" of the drug as an analgesic by substantial numbers of patients and physicians in varying specialties. Experience should be obtained in outpatient populations if the analgesic is intended for oral administration. In addition to adequate and well-controlled clinical studies, well-documented uncontrolled clinical trials have a place in the Phase 3 investigation of an analgesic. Appropriate laboratory tests should be performed at regular intervals during chronic administration. The tests and intervals should be based on animal and earlier human experience with the drug and other similar drugs. As experience increases, the testing might become less intensive; however, if a particular reaction, previously not seen, shows up in some trials, more intensive laboratory testing may be appropriate.

The dose and dosing intervals chosen for Phase 3 repeated-dose therapeutic and tolerance studies should be predicted on the basis of the controlled Phase 2 studies. These dosing intervals constitute the regimens tentatively identified for the package insert and are chosen to provide analgesia comparable

to that produced by approved standard analgesics. For example, if a 100 mg dose of the test drug has been shown in Phase 2 studies to produce analgesia comparable in intensity and duration to a dose of 650 mg of aspirin, Phase 3 studies should be designed to establish the safety of at least 600 mg total daily dose of the test drug, i.e., 100 mg every 4 hours. On the other hand, if Phase 2 studies had established that the test drug had a longer duration of action than aspirin and 100 mg of the test drug produced analgesia at 6 hours comparable to that produced by 650 mg of aspirin at 4 hours, then Phase 3 studies demonstrating the safety of 400 mg total daily dose, i.e., at least 100 mg every 6 hours, would be appropriate. In both cases, the appropriate control treatment would be 650 mg of aspirin every 4 hours.

1. Patient Population--Types of Pain to be Studied

An effort should be made to explore the use of the analgesic in various types of pain. Entrance criteria for these studies should be based on the anticipated use. Patients should not be excluded on the basis of age, sex, other drugs, or other medical conditions that are likely to be present concurrently and which are not contraindicated at the current stage of development, or for which there is no reasonable basis to assume that there will be an adverse reaction with the test drug or the control drug. Evidence that an agent has analgesic activity in pain of several different etiologies will justify "general purpose" analgesic labeling unless special considerations indicate that this is not appropriate. On the other hand, the inclusion of specific labeling indications for preoperative medication, for support of anesthesia, for obstetrical analgesia, or for dysmenorrhea will require suitably designed studies in these particular patient groups.

2. Multidose, Short-Term Therapy

A new drug application should include studies using multiple doses of the drug in patients requiring short-term therapy. These studies should be randomized, parallel, double-blind, controlled trials in patients for whom the drug is ultimately intended.

The pain models used should be those which typically require several days of therapy. Examples include postoperative pain, posttraumatic pain, sore throat pain, postoral surgical pain, and cancer pain. These studies should include a positive control and may include a placebo as long as rescue medication is available. It may be possible to extend single-dose efficacy studies to incorporate multiple-dose treatment evaluation in some models.

The design of these trials could incorporate either PRN or fixed dosing. In either case, available pharmacokinetic and pharmacodynamic data, as well as data from previous single-dose trials, provide the background for establishing a dosing interval. PRN trials could assess, or test, dosing interval information that might be helpful in labeling. Because continuous hourly pain measurement may not be feasible with multiple dosing, a dose-to-dose global evaluation of analgesia could be used. A daily global assessment of analgesia could also be utilized.

The intent of these multiple-dose studies is the development of data using patients and dosage regimens that are appropriate for (or consistent with) the intended clinical use and labeling of the drug.

The analysis of data from these studies should include efficacy, safety, and dosing frequency. Because of inherent increased variability, these repeat-dose pain models may not provide the degree of assay sensitivity achievable with single-dose analgesic studies. However, these models do offer an assessment of a drug under circumstances more closely resembling intended use.

3. Chronic Administration

Because it usually can be anticipated that an analgesic will be used in chronic as well as acute pain states, an effort should be made to gain well-documented evidence of the effects of chronic use, even though some of this may not be from controlled trials. The state-of-the-art of the controlled evaluation for effectiveness of chronic analgesic administration (i.e., for periods greater than 2 to 3 days) is much less developed than the methodology for single-dose studies, and fewer controlled chronic studies have been performed. This type of study may be designed as either a parallel or crossover, double-blind comparison of the test drug with an appropriate standard and may include the option of titrating each drug within certain limits according to the needs of the patient. Alternatively, some studies may be done with a historical control, but this design obviously complicates the interpretation of treatment-emergent adverse effects. The focus of these studies will be on providing documentation of "clinical acceptability" and safety of the test drug rather than providing pivotal proof of efficacy. Since fewer patients are available who require prolonged administration of injectable analgesics than require chronic oral analgesic administration, documented experience with parenterally administered analgesics may be less extensive than with oral dosage forms regarding both number of patients and duration of administration.

Narcotic and narcotic antagonist-type agents should be scrutinized for evidence of tolerance development. The development of physical dependence to narcotic-type agents may sometimes be demonstrated through withdrawal or sensitivity to challenge with an antagonist drug. Lack of evidence of physical dependence and/or instances of abuse of an agent in chronic trials is, in itself, not sufficient to predict abuse liability of a new analgesic. Clinical pharmacology studies should be used to specifically assess the behavioral, subjective, and physiological response to the narcotic analgesic in comparison to an appropriate reference standard of known liability. Characteristics to be investigated for the narcotics and agonist-antagonist drug classes that might be suggestive of abuse liability, include the following: precipitation of withdrawal symptoms in opioid-dependent subjects; existence of a ceiling on, and magnitude of, acute antagonist effects; relative intensity of, and potential for, physical dependence; production of euphoria and/or collateral dysphoria.

In addition to standard safety parameters, these chronic studies should include surveillance of systems in which drug-induced abnormal findings have been demonstrated in animal studies or

adverse effects have been demonstrated in the Phase 1 and 2 studies in man. These studies should be regarded as an opportunity to test the adequacy of the recommendations that are proposed for the package insert.

i. Peripherally Acting or NSAID Oral Analgesics. It is recommended that the safety of peripherally acting or nonsteroidal anti-inflammatory oral analgesics be evaluated in studies designed to provide data on sufficient patients who receive the test drug on a regular basis for at least 6 months. These studies should include data on patients who have received the test drug under randomized, double-blind conditions using as a reference patients receiving an appropriate standard drug. Patients with degenerative joint disease (osteoarthritis) may serve as a suitable population for the evaluation of the chronic administration of a peripherally acting or NSAID analgesic. In addition, experience should be obtained in patients with pain of other etiologies for periods of time appropriate for the condition or clinical use anticipated.

ii. Centrally Acting Oral Analgesics. The safety of centrally acting oral analgesics should be supported by studies in sufficient patients who have received the test drug on a regular basis for at least 1 month to identify adverse reactions in the 1 to 3% range. Sufficient patients should receive the test drug in a double-blind comparison with a standard centrally acting analgesic to identify threefold to fivefold differences in adverse effects in the 1 to 3% range.

When feasible and consistent with good medical practice, patients should continue to receive the test drug for at least 3 months.

In addition, experience should be obtained in patients with pain of various causes who receive the drug for periods of less than 1 month or who receive the drug intermittently for varying periods, and, if appropriate, as a supplementary analgesic in patients receiving NSAIDs for the treatment of rheumatic disease.

iii. Oral Combination Analgesics. The safety of an analgesic combination, made up entirely of ingredients that have already been approved for marketing, should be supported by studies in patients who are given the combination on a regular basis for at least 1 month; the sample size should be large enough to allow a fair assessment of the safety profile of the combination (see 14, page 17, as well as 16, page 19, for special considerations regarding combination analgesics).

4. Children and Women of Childbearing Potential

Children may be included in Phase 2 or Phase 3 studies. There is no evidence to indicate that adolescents respond differently to analgesic drugs than adults. There are few published controlled analgesic studies in children, but the methodology for such studies is being developed and the importance of evaluating analgesics in this patient group is obvious.

Women of childbearing potential, who are not practicing contraception, may be included provided that all three segments of the Animal Reproductive Study Guidelines have been completed and the results from animal tests are satisfactory. If the agent is recommended for obstetrical pain, followup for potential adverse effects on the infant during labor and after delivery is necessary.

D. Special Studies

1. Drug Dependence Liability

"Peripherally-acting" analgesics that are clearly aspirin-like in pharmacologic profile do not need to be specifically evaluated for drug dependence liability unless evidence of mood-altering effects accumulated during clinical evaluation indicates that such testing is advisable. Analgesics chemically or pharmacologically related to known dependence-producing drugs and those unrelated to existing analgesics should be tested in animals for dependence-producing properties.

2. Side Effect Liability

Studies comparing the test drug with an appropriate standard at equi-analgesic doses for the purpose of determining relative side effect liability are required. The types of studies involved will, by necessity, depend on the category of drug being investigated, and some may be performed in normal volunteers as well as in patients. Narcotic and narcotic antagonist type agents should be studied for their effects in producing respiratory depression and cardiovascular instability. Likewise, they should be compared in terms of their ability to produce subjective effects.

If the agent is a narcotic antagonist, an effort should be made to determine if, and at what dose, it is capable of precipitating abstinence, or withdrawal symptoms, in patients physically dependent on narcotics.

Aspirin-like agents should be studied from the standpoint of their ability to produce evidence of gastrointestinal irritation as well as to ascertain gastrointestinal blood loss and symptoms referable to the gastrointestinal tract and to alter blood coagulation.

Specific studies of drug interactions should be performed with drugs likely to be administered concurrently to the patient population for which the analgesic is to be indicated. If the agent in question has other prominent pharmacologic properties, it is generally necessary to conduct special studies delineating such effects whenever they can be anticipated to have relevance for safety.

IV. LABELING CONSIDERATIONS

For a number of years, both opioid and nonopioid analgesics have been labeled with indications for "mild, moderate, moderately severe, or severe" pain. These terms, which patients use to describe the intensity of their pain both from minor causes requiring weak analgesics as well as pain that requires strong analgesics, are not very useful in indicating to clinicians when or how to use a new analgesic. Recently, FDA has initiated a new approach to analgesic labeling in which the indication is: "For the management of pain (see Clinical Pharmacology)." In the Clinical Pharmacology section, the clinical trial results are briefly described in terms of onset, peak effect, and duration of effect for the test and standard drugs. Clinical studies, particularly in Phase 3, in patients for whom the drug is intended should provide suitable trials for this purpose. Doses of the standard drugs used for comparison should be appropriate. If such studies are not available or the studies that were done use less than optimal doses of the standard drug, it will delay approval until appropriate comparative study information is available.