
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



**guidelines for the clinical
evaluation of
Local Anesthetics**

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

**GUIDELINES FOR THE CLINICAL EVALUATION
OF
LOCAL ANESTHETICS**

**PRINTED SEPTEMBER 1977
REVISED MAY 1982**

**This publication may be reproduced and distributed 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:**

**Dockets Management Branch (HFA - 305)
Docket Number - 82D-0116
Rm 4 - 62
5600 Fishers Lane
Rockville, Maryland 20857**

For further information regarding the guidelines please contact:

**DIRECTOR
DIVISION OF SURGICAL DENTAL DRUG PRODUCTS
BUREAU OF DRUGS
FOOD AND DRUG ADMINISTRATION
5600 FISHERS LANE
ROCKVILLE, M.D. 20857**

ABSTRACT

The Food and Drug Administration, with the assistance of its scientific Advisory Committees and other outside consultants, the American Academy of Pediatrics' Committee on Drugs, and consultants to the Pharmaceutical Manufacturers' Association has developed guidelines for the clinical evaluation of new drugs. These guidelines present acceptable current approaches to the study of investigational drugs in man, and pertain to Phases I through III of the investigation. They represent generally acceptable principles for arriving at valid conclusions concerning safety and effectiveness of new drugs, as well as the views of outstanding experts concerning appropriate methods of study of specific classes of drugs.

The FDA welcomes comments on the guidelines, and expects to keep them current by review and update at approximately two-year intervals.

FOREWORD

The purpose of these guidelines is to present acceptable current approaches to the study of investigational drugs in man. These guidelines contain both generalities and specifics and were developed from experience with available drugs. It is anticipated that with the passage of time these guidelines will require revision. In order to keep them current a re-review will be performed approximately every 18 to 24 months.

These guidelines are not to be interpreted as mandatory requirements by the FDA to allow continuation of clinical trials with investigational drugs or to obtain approval of a new drug for marketing. These guidelines, in part, contain recommendations for clinical studies which are recognized as desirable approaches to be used in arriving at conclusions concerning safety and effectiveness of new drugs; and in the other part they consist of the views of outstanding experts in the field as to what constitutes appropriate methods of study of specific classes of drugs. In some cases other methods may be equally applicable or newer methods may be preferable, and for certain entirely new entities it is possible that the guidelines may be only minimally applicable.

Under FDA regulations (21 CFR 10.90(b)) all clinical guidelines constitute advisory opinions on an acceptable approach to meeting regulatory requirements, and research begun in good faith under such guidelines will be acceptable by the Agency for review purposes unless this guideline (or the relevant portion of it) has been formally rescinded for valid health reasons. This does not imply that results obtained in studies conducted under these guidelines 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.

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 and of the Pharmaceutical Manufacturers Association; in these cases the guidelines were reviewed and revised, as appropriate, by FDA's Advisory Committees.

The general guidelines for the evaluation of drugs in infants and children and most of those for study of various drug classes in children were developed by the Committee on Drugs of the American Academy of Pediatrics (AAP). Some of the pediatric guidelines for specific classes were written by FDA's Advisory Committees. There was cross review and comment on the pediatric guidelines by both the Committee on Drugs of the AAP and FDA's Advisory Committees.

The Bureau of Drugs of the FDA wishes to thank the many individuals who devoted so much time and effort to the development of these guidelines.

J. Richard Crout, M.D.
Director
Bureau of Drugs

Marion J. Finkel, M.D.
Associate Director for
New Drug Evaluation
Bureau of Drugs

GUIDELINES FOR THE CLINICAL EVALUATION OF LOCAL ANESTHETICS

"General Considerations for the Clinical Evaluation of Drugs" is an important companion piece and should be reviewed prior to reading these guidelines. It contains suggestions which are applicable to investigational drug studies for most classes of drugs and enables elimination of repetitious material in each of the specific guidelines.

I. INTRODUCTION

The Nature of the Recommendations

Those items designated as required may be construed as minimal acceptable standards. Those designated optional represent maximal achievable goals. The category of recommended falls between these extremes and should be interpreted by the individual investigator. Even those items labeled required may be complied with by other tests or techniques which provide equivalent information.

Guide to Symbols

- ** - Required
- * - Required--except as noted
- + - Recommended
- x - Optional

II. CLINICAL PROCEDURES

PHASE I

A. Initial Determination of Local Anesthetic Activity and Potential Tissue Irritation

- 1.** Intradermal wheals in a small number of volunteers using a constant volume and varying the concentration of the local anesthetic agent (a minimum of three concentrations). The concentrations selected for these initial studies should be based on animal tests for local anesthetic activity in which the test compound is compared to a similar standard agent such as, but not limited to, lidocaine, mepivacaine, procaine, tetracaine, bupivacaine. If the local anesthetic agent is to be combined with a vasoconstrictor drug and/or preservative, studies should be repeated using various concentrations of the local anesthetic agent in the proposed pharmaceutical preparation. Onset and duration of sensory anesthesia should be evaluated by a standardized technique. Local irritation should be assessed by determination of inflammation, swelling or necrosis in area of injection during and following the block. The initial studies can be "open label," but later studies should be conducted under double-blind conditions utilizing both a placebo and a standard local anesthetic agent for comparison.

2.** Infiltration - for minor surgical procedures

3.* Single Nerve Block - Limited peripheral nerve blocks (e.g., digital nerve, ulnar nerve or intercostal nerve) should be performed in human volunteers or patients, employing a constant volume and varying the concentration of the local anesthetic agent (with and without a vasoconstrictor drug, if applicable). These studies should be concerned with (a) safety, and (b) the optimal effective concentrations of the test agent. Initially blocks for sensory analgesia alone should be performed. Sensory analgesia should be evaluated by a standardized method to determine reliability, onset and duration of analgesia. Local irritation potential should be evaluated by observing as described above the area of block, including post-block symptoms and function. If the test compound demonstrates adequate sensory anesthetic activity without local irritation, additional blocks of other peripheral nerves can then be performed. In these studies sensory, motor and sympathetic activity, where possible, may be evaluated. Sensory analgesia should be determined by a standard technique. Motor block may be evaluated by techniques such as finger motility or electromyography.

4.+ Sympathetic block may be evaluated by measurement of skin temperature, psychogalvanic response, or skin resistance.

These studies also should be performed under controlled doubleblind conditions using a standard local anesthetic agent for comparison and utilizing bilateral blocks in the same subject simultaneously. Local neural toxicity and tissue irritation also should be evaluated for symptoms and function at 24 to 48 hours following injection in these studies. The injected area should be examined for signs such as inflammation, swelling, necrosis, neuritis or persistent anesthesia.

B.+ Tolerance Studies

Intravenous infusion of carefully selected concentrations and volumes in healthy volunteers with measurements of blood levels. The concentration of drug, total dose and duration of infusion period (usually 2 to 5 minutes) should be based on the relative toxicity of the test drug in animals as compared to a standard agent. If feasible, measurements of blood levels should be performed with a method which is specific and sensitive for the test compound, e.g., chromatography. Blood levels should be determined for a sufficient length of time to establish the half-life of the investigational compound in blood.

Measurement should be made of CNS function (electroencephalograms, state of consciousness, sensorium), blood pressure, heart rate, and ECG.

Studies should be a dose-response type in order to establish, if possible, relationship between dose administered, blood level and changes in CNS, cardiovascular or other organ system functions.

PHASE II

A. Patients

Clinical nerve blocks should be performed in adult male patients, and adult female patients of non-childbearing potential for relief of pain related to surgery or of pathologic origin. Ordinarily, these patients should have no systemic disease or only mild systemic disease. Patients with pathologic pain and systemic disease, who would normally be given nerve blocks, would be candidates for a block with this particular agent, if it has been demonstrated by this point not to have serious systemic effects which would be a threat to these particular patients.

B. Dosage

Dosage of agent and complexity of technique should be graded and based on experience in Phase I.

C. Anesthetic Procedures

- 1.* Infiltration
2. Peripheral nerve blocks, e.g.,
 - a. Intercostal nerve block (comparison with standard agents is recommended)
 - b. Brachial plexus block, sciatic-femoral block
 - c. Paravertebral, somatic, face blocks, etc.
 - d. Obstetrical studies should be deferred to Phase III
3. Central blocks
 - a. Extradural (peridural, epidural)
 - b. Subarachnoid (if agent is intended for spinal anesthesia)
4. Sympathetic nerve blocks (e.g., cervicothoracic, stellate ganglion, lumbar sympathetic)

These various procedures are taken as representative of the most common type of nerve blocks performed and should afford substantial evidence of local anesthetic capabilities. These blocks should be performed under controlled clinical conditions. A standard local anesthetic agent should be employed as a source of comparison and the studies should be conducted as double-blind, randomized studies when feasible.

- 5.x Intravenous regional anesthesia (this use is optional), but clinical studies are required if the new drug is intended for this use).

D. Effectiveness

- 1.** Pain relief (Determination of anesthesia in a series of patients will provide data to calculate frequency of adequate anesthesia.)
2. Onset, duration and spread of sensory and motor anesthesia as determined by a standardized method
3. Degree of muscle relaxation

E. Safety

- 1.** Signs of systemic toxicity as determined by clinical observations, measurement of pulse, blood pressure and standard clinical chemistries
2. Local tissue irritation
3. Local neurotoxicity as evaluated by completeness of recovery from anesthesia. When done for patient's benefit, neuroradiography should be included in complication reports.
4. Unusual systemic effects

F. Other Considerations

- * During the course of these studies the dosage range (volume and concentration) required for satisfactory performance of the various anesthetic procedures should be determined. In addition, if the agent is to be used for multiple dose techniques, the limits of dose rate, i.e., the minimal time interval between successive doses should be determined and the potential accumulation of the new agent evaluated. The requirements of a vasoconstrictor drug should also be determined, if applicable.

If the agent is intended for dental anesthesia, controlled studies should be carried out in which the agent is used for infiltration anesthesia and peripheral nerve blocks (e.g., mandibular nerve block). Comparison should be made with a standard dental anesthetic agent utilizing double-blind techniques, when possible. These studies should determine dosage requirements, onset, spread, duration of soft tissue and pulp anesthesia, as well as frequency of satisfactory anesthesia in patients undergoing clinical dental procedures. Signs of possible local irritation should be observed.

G. Absorption Studies

- + Blood level determinations of the investigational local anesthetic compound should be carried out following its use for the various categories of clinical anesthetic procedures outlined above. Blood or plasma concentrations should be determined in selected patients utilizing a specific and sensitive technique such as gas chromatography. Information to be obtained should include:
 1. Rate of absorption from various sites of administration and at various dosage levels
 2. Half-life of agent in blood following peak blood level
 3. Cumulative potential during intermittent multiple dose techniques
 4. Effect of vasoconstrictor drugs (if applicable) on rate of absorption and disappearance from blood
 5. Protein binding

PHASE III

Phase III is directed toward the assessment of the investigational drug under conditions under which it will be used in clinical practice. At this time, the effects of a multiplicity of variables must be evaluated and studied, e.g., different types of nerve blocks, adverse reactions observed, and the relationship between the new agent and other drugs commonly used before, during, and/or after surgery.

A.**Experimental Design Considerations

In designing the study, consideration should be given to the following:

1. Specification of patient population with respect to identifiable subgroups of homogeneous subjects
2. Specification of important stratifications of subjects with respect to control groups
3. Specification of hypotheses to be tested and variables to be compared
4. Specification of statistical risks one will allow in the study comparisons (e.g., Type 1 and Type 2 errors) or the precision in estimates of anesthetic effects one will expect
5. Specification and justification for study sample sizes

B. Anesthetic Procedures

- 1.** Infiltration
2. Peripheral nerve blocks (e.g., intercostal, brachial plexus, sciatic-femoral, paravertebral, digital blocks, etc.)
3. Central blocks (extradural or subarachnoid)
4. Sympathetic nerve blocks (e.g., cervicothoracic, stellate ganglion, lumbar sympathetic)

The studies should be documented by completed clinical anesthesia records.

C. Safety and Effectiveness

- ** The factors to be measured for safety and efficacy should be similar to those outlined for Phase II studies. Based on the results obtained in Phase II studies, it should be possible to standardize the studies performed during Phase III. For example, the frequency of observations and measurements of safety and anesthetic effectiveness should be standardized to facilitate the comparison and analysis of results obtained by different investigators. Sufficient patients as determined by the specific agent under investigation should be studied under carefully controlled conditions per category of nerve block to provide adequate data for the evaluation of the safety and efficacy of a new local anesthetic compound. Data collection should make possible the assessment of the relationships existing between the local anesthetic agent employed and other drugs commonly used before, during, and/or after surgery (e.g., preanesthetic medication, other anesthetic agents, anesthetic adjuncts, and drugs which patients may commonly take on a chronic basis, such as diuretics and tranquilizers).
- ** Patients should be followed for symptoms of neuritis and tissue damage for longer than the duration of anesthesia, and the duration of follow-up should be noted.
- + Tests for methemoglobin should be performed prior to anesthesia, at specified intervals during anesthesia and once after recovery in a representative sample of patients receiving significant quantities of drug.

D. Obstetrical Studies (Needed for consideration of use in obstetrics)

- ** Before the investigational agent is used for deliveries adequate animal studies should be done to measure placental transfer and the effect of the agent on the neonate. When used in clinical trials, studies should be conducted to determine:

- 1.** Blood levels, if measurable, following administration of the agent for various anesthetic procedures employed prior to delivery
- 2.** Effect of new agent on labor
- 3.** Placental transfer of the local anesthetic agent following its use for various anesthetic procedures (maternal and umbilical blood samples at delivery)
- 4.** Effect on physiologic status of fetus during labor and delivery

** Required

- a. Serial heart rates
- b. One and 5 minute Apgar scores
- c. Time to sustained respiration

+ Recommended

- a. Fetal ECG

x Optional

- a. Blood gases and pH (scalp vein)

If fetal depression is observed, the infant should be monitored for as long as indicated.

- 5.x In procedures where large amounts of the agent are used, the disappearance rate of the agent in the blood of infants after the block, as determined by multiple blood samplings.

- 6.** Short term neonatal neurobehavioral studies

E. Dental Anesthesia: Studies should be carried out utilizing the anesthetic procedures employed in dentistry.

- 1.** Infiltration

- 2.** Peripheral nerve blocks (e.g., mandibular blocks)

Sufficient patients should be used to provide a proper evaluation of each anesthetic procedure. The dosage requirements (concentration and volume) and vasoconstrictor drug requirements (if applicable) should be determined for both operative and restorative dental procedures. Measurements of safety and effectiveness as outlined in phase II dental studies should be performed.

F. Other Considerations

1. Concomitant disease states

- + During the course of clinical investigations of a new local anesthetic compound it is recommended that data should be evaluated for relationship between specific disease states (e.g., cardiovascular, renal, hepatic abnormalities) and the safety and efficacy of the new agent as indicated. For example, in patients with heart failure or in shock states the absorption, distribution, metabolism and excretion of an agent may be significantly altered and thus affect the safety and anesthetic effectiveness of the agent. Thus, consideration should be given to possible monitoring of blood levels of the anesthetic agent (if feasible) in selected patients in these broad disease categories to predict possible alterations in the safety and efficacy of the anesthetic agent.

2. Use as a topical anesthetic

If the investigational agent is intended for use as a topical anesthetic agent, controlled studies should be conducted to evaluate:

a. Safety

(1)** The potential local irritating properties of the topical local anesthetic preparation (e.g., ointment, spray, jelly, etc.) should be carefully evaluated and compared to a standard topical local anesthetic preparation.

(2)+ The rate of absorption from various sites of administration and for the various dosage forms should be determined by measurements of blood levels of the local anesthetic agent. This should provide data on the potential systemic toxicity of the topical anesthetic dosage form.

b.** Effectiveness - Depending on the potential indication for use the effectiveness of a topical local anesthetic preparation should be evaluated under controlled conditions utilizing either a placebo or standard topical local anesthetic preparation as a reference. The measurements of local anesthetic efficacy should include:

(1) Frequency of satisfactory anesthesia

(2) Onset of anesthesia

(3) Duration of anesthesia

c. Other Considerations

****** Consideration should be given to site of intended topical application (e.g., skin, mucous membranes, eye, ear, etc.). If the agent is intended for ophthalmological use, special attention must be given to potential corneal irritation and several evaluations (e.g., slit-lamp examinations) should be made prior to, during, and following application of an anesthetic agent on the surface of the eye. If the agent is intended for repetitive use, especially on skin, the potential for local irritation and/or local allergic phenomenon should be evaluated. If the active agent in the topical anesthetic preparation is an approved local anesthetic agent, it should be possible to determine readily by means of well-controlled studies whether the agent is safe and effective when applied topically. If the active agent in the topical anesthetic preparation is a completely new chemical compound, more extensive studies will be required to demonstrate safety and efficacy.

G. Data Reporting

****** In designing the plan for analysis and reporting of the data and findings from completed studies, consideration should be given to the following:

1. Data and findings should be reported separately for each protocol, investigator, clinic, etc.
2. Summary tables of selected parameters should be presented for all relevant subgroups of subjects studied so that appropriate comparisons can be made. For example, time to recovery, incidence of nausea or vomiting, blood pressure, respiratory rate, body temperature, etc. should be displayed by factors such as age, sex, severity of surgery, duration of anesthesia, etc.
3. For all safety parameters, a display of appropriate pre- and post-treatment parameters measured and an appropriate statistical evaluation of the changes in pre- to post-measurements.
4. A detailed documentation of the statistical methods employed along with the conclusions based on the analysis.
5. A well organized and documented data base (including data on all subjects entered into the study and on all measurements taken).



UNITED STATES GOVERNMENT PRINTING OFFICE
DIVISION OF PUBLIC DOCUMENTS
WASHINGTON, D.C. 20402

OFFICIAL BUSINESS

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF H.H.S.
HHS 396



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
5600 Fishers Lane
Rockville, Md. 20857

HHS Publication No. (FDA) 82-3053