

Guidelines for the Clinical Evaluation of Antidementia Drugs

First Draft

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1. Purpose of the Guidelines:

This Guideline is one of a series of documents published by the FDA to assist sponsors in their development of new drug products. This particular guideline, dealing exclusively with antidementia drugs, provides detailed information about the nature of and basis for agency policies that may affect the scope and pace of premarketing product development.

These guidelines are intended primarily to provide advice about matters and issues relating to the planning, design, conduct and the interpretation of clinical investigations, investigations that must serve as the primary sources of evidence supporting claims for the safety and efficacy of new drug products.

The advice offered reflects what experts working in the field believe are scientifically sound approaches to a number of issues that in the past have posed difficulties for the developer of antidementia drugs. Hopefully, the sponsor who heeds the advice and suggestions offered will find the demanding task of commercial drug development much facilitated.

1.1. *Definition of Dementia:*

sanguine assumptions and appeals to biologic plausibility, the drug has of unknown etiology that ordinarily causes a progressive, irreversible decline in intellectual and cognitive abilities. Although the syndrome of dementia presumably has many causes, this Guideline is intended primarily to provide advice about developing treatments for patients who would be deemed to suffer from Alzheimer's Dementia¹

However, many of the principles enumerated in the guideline apply equally well to other types of chronic dementing illness. (e.g., multi-infarct dementia).

1.2. *The nature of acceptable antidementia drug claims:*

The intended therapeutic use and/or claim made for an antidementia drug affects the nature of its development and testing. Clearly, a drug intended to prevent and/or reverse the dementing process will be evaluated under very different testing conditions than one intended to suppress psychotic behavior in an institutionalized, end stage patient.

These guidelines focus primarily upon treatments intended to affect the "core" phenomena of Alzheimer's Dementia. Although there are some minor disagreements about the identity of the core phenomena and their relative importance, experts generally agree² that a treatment cannot be considered to exert an 'antidementia' action unless it beneficially affects a demented patient's ability to learn new and retrieve old, previously learned, information.

This does not, of course, preclude the development of drugs that affect other aspects of the dementing process (i.e., failed self care, disturbed mood, loss of control over impulses, etc.), but it does restrict the nature of the drug effects that will be granted an unmodified antidementia indication. Of particular importance, claims for actions artificially tied to dementia (i.e., so called 'pseudospecific' claims will not be allowed.³

A distinction is often made between symptomatic and definitive treatments; either are acceptable claims for an antidementia drug. Unfortunately, until the etiology and/or pathogenesis of the dementing process is fully understood, it seems unlikely that a definitive treatment for Alzheimer's will be developed.

More probably, antidementia drugs, at least in the near future, will be those that cause an improvement in, or slow the rate of deterioration of, the various functions (memory, reason, etc.) that fail increasingly as the dementing process progresses.

1.3. FDA's Regulation of Clinical Drug Testing: an overview:

The Federal Food, Drug and Cosmetic Act, our domestic drug regulatory law, instructs the FDA to 'Promulgate' regulations governing the conditions under which clinical investigations of new drugs may be conducted⁴. The Act makes plain that Congress, in issuing this instruction, sought the implementation of a system of drug regulation that would protect subjects participating in clinical investigations from unreasonable and/or unnecessary risks to their health and safety.

In view of this mandate, FDA's regulations and policies governing the clinical testing of new drugs must "assure the safety and rights of subjects." However, because the development of effective treatments for serious illnesses such as Alzheimer's Dementia is very much in the interests of the public health, FDA's regulations and policies are also designed to enhance the "quality" of clinical investigations that are intended by sponsors to serve as sources of evidence supporting their New Drug Applications.

Thus, proposals to conduct clinical investigations are evaluated not only in light of the risks they impose upon human subjects, but for their capacity (i.e. by virtue of their design and protocol requirements) to provide a valid assessment of the therapeutic (or diagnostic) potential of the experimental drug under test. Accordingly, the regulatory assessment of proposed research protocols takes into account the nature of the illness for which the treatment is being developed, the availability of alternative treatments, all information relevant to the therapeutic potential and toxicity of the new drug, the type of clinical trial design proposed, and the adequacy of the plans for the actual conduct of the experiment (e.g., statistical power, nature of patient entry criteria, validity and reliability of assessment measures, etc.). In sum, the goal of regulation is to ensure that clinical research is conducted using valid designs under conditions that minimize the risk to subjects.

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2.1. *The Strategy and Tactics of Drug Development:*

2.1.1. Essential prerequisites of clinical drug testing

Prior to its use in humans, an investigational drug substance is evaluated in a battery of preclinical tests (i.e., in vitro, ex vivo, and in vivo tests) intended to identify its potential to cause structural injury and/or interfere with normal physiologic functions. Ordinarily, in vivo preclinical tests are conducted under conditions more extreme (i.e., in terms of duration and amount of drug) than those to which human subjects will be exposed. Clinical testing with a new drug is only initiated if the evidence adduced in an appropriate preclinical test battery provides reasonable assurance that the use of the drug will not cause immediate, irreparable harm or injury. 5

2.1.2. Early clinical testing

The pace of expansion of clinical testing (i.e., in terms of the total current and cumulative numbers of individuals exposed to an investigational drug) and the conditions under which clinical testing is permitted (i.e., in terms of dose, cumulative dose, duration of exposure, setting for the experiment, quality and intensity of medical monitoring of subjects, etc.) is governed by the nature of information developed in clinical and preclinical experiments.

Clinical testing ordinarily begins with the exposure, under closely monitored medical supervision, of a few healthy individuals to single, comparatively low, doses of a drug⁶. If no serious untoward events or physiologic disturbances occur under these initial conditions, additional subjects are exposed to higher and/or repeated doses; in this manner, the common untoward and toxic effects associated with the use of the drug are identified. If dose (i.e., or equivalently, drug plasma concentration) dependent toxicities do not preclude it, volunteers are often exposed to doses of the drug that exceed those estimated (e.g., from preclinical data, or non-domestic clinical reports) to be necessary to achieve the desired therapeutic response in patients⁷. In this manner, a clinical pharmacological/physiologic/toxicologic profile of a new drug is compiled. As noted, the plasma (or effect compartment) drug concentrations at which these various drug associated phenomena occur is, ideally, also recorded, and this information, taken together with the results of additional, concomitantly conducted, preclinical studies, then serves as an ever widening informational base for decisions regarding the subsequent development and testing of the drug.⁸

2.1.3. The early demonstration of efficacy:

The testing of an experimental drug of undocumented value cannot be extended indefinitely. Because exposure to virtually any pharmacologically active drug imposes some potential risk, the exposure of large numbers of subjects to a drug that may be therapeutically ineffective or to an effective drug administered at subtherapeutic doses cannot be medically or ethically justified. Consequently, regulatory policy requires sponsors to document the efficacy of an investigational drug and characterize the conditions under which it expresses its therapeutic effect as early in the course of its development as possible.

In regard to the development of drugs for the treatment of dementia, this policy has important implications. Before the efficacy of an antidementia drug is documented (i.e., during phase 1 and early phase 2), open studies are justified only to the extent necessary to establish its maximum safely tolerated dose in volunteers and typical patients. Once this upper dose (or plasma concentration) range is delimited, there is no justification for additional uncontrolled use of the investigational drug because the spontaneous variability in the course of the dementia (in any given patient) makes uncontrolled investigations of efficacy pointless. Of course, after the efficacy of a drug is documented, open studies may be a preferred way to gain insights into the toxicities associated with its use (i.e., in Phase 3). This policy derives from the view that the exposure of large numbers of individuals to drugs of unestablished therapeutic value is an ethically arguable undertaking.

For the reasons just given, once a reasonable estimate for the range of doses and/or drug plasma concentrations presumed necessary to achieve a therapeutic effect has been obtained⁹ prospectively randomized controlled trials capable of definitively documenting the efficacy of the putative antidementia agent must begin. Again, because of the marked variation among patients with dementia (i.e., in terms of course, rate of deterioration in function, etc.), it is essential that these controlled trials compare one or more fixed doses (or narrow plasma concentrations) of the experimental drug with a placebo control¹⁰.

In the absence of an established treatment for dementia, a standard drug cannot be used as a control, per se; however, there is no objection to comparing a putative antidementia drug with another investigational agent thought to possess anti-dementia activity so long as the comparison includes randomized and blinded assignment of patients to a placebo control as well.

In sum, the process of drug development envisioned in regulations is dynamic and open-ended, the program for the clinical testing of a new drug undergoing continual iterative adjustment as new insights into its pharmacology, pharmacokinetics, risks, and therapeutic benefits are gained.

2.2. *The Ultimate Goal of Drug Development*

By law, only safe and effective drug products can be marketed, but developing a product that can be judged 'safe for use' and 'effective in use' involves more than presenting results from clinical studies that document the product's superiority to some control treatment and that show that it can be administered with relative safety to a substantial number of patients.

Information and data must also be developed that will permit the sponsor to draft reliable instructions for the use of the product in the individual patient. Because response to a drug is a function of pharmacokinetic and pharmacodynamic factors that vary among patients, a single dosing regimen will not ordinarily be suitable for every patient.

To the extent that it is possible, therefore, sponsors should evaluate how age, race, sex, weight, concomitant medications and state of overall health affect response to treatment. This evaluation can be facilitated by assessing the extent to which these patient attributes affect population based estimates of the product's pharmacokinetic parameters (e.g., volume distribution, plasma clearance, etc.).

In sum, the ultimate goal of the government's regulation of drug product development is the marketing of safe and effective drug products with labeling that provides information that will allow the practitioner to individualize the regimen for the drug's administration for those physiologic and demographic attributes that are known to affect treatment response.

3. Phases of drug development

3.1. *Phase 1*

The goals of Phase 1 of drug development are, for most practical purposes, independent of the intended use of a drug. Consequently, the reader is also referred to the agency's General Guidelines for Drug Development which provide a more detailed discussion of this first phase of clinical testing.

Phase 1 is the period during which the common untoward effects of a drug in humans are identified and initial estimates of its maximum tolerated dose (or plasma

concentrations) are developed. Phase I clinical pharmacology studies also provide an opportunity to characterize the disposition of a drug (i.e., obtain data on its absorption, distribution, metabolism and elimination (its ADME). Data obtained during single, rising dose and repeated multiple dose human safety/tolerance--studies can be used to estimate the fundamental parameters that depict the pharmacokinetics of a drug.

These estimates along with observations linking common untoward clinical effects and plasma concentrations of the drug and its metabolites are invaluable to those planning subsequent clinical trials. The value of acquiring this information early cannot be over emphasized; it is especially important in circumstances where the drug being developed has an intrinsically narrow therapeutic ratio. In such circumstances, knowledge of a drug's pharmacokinetic properties and maximum tolerated plasma levels may permit the sponsor to devise dosage formulations or dosing regimens that will substantially reduce the overall incidence of dose or concentration dependent untoward effects, effects that might ordinarily preclude the further development of the product.

Phase I is also the best time to discover whether or not a drug exhibits atypical pharmacokinetic properties (i.e., nonlinear kinetics, concentration or time dependent clearance, etc.). Again, acquiring this information early in development may allow sponsors to make timely decisions about the drug's potential as a commercial drug product.

In any event, by the end of phase 1, a sponsor should have exposed sufficient numbers of subjects to single and multiple doses of the drug to have identified the more common acute toxicities and physiologic actions of the drug up to doses (or plasma levels) exceeding those likely to be used (or be obtained) during phase 2 controlled trials.

To the extent permitted, the relationship between dose and/or plasma concentration and the outcomes observed should be assessed to determine if either dose, or plasma concentration predict the phenomena observed. At a minimum, enough basic information about the ADME of the drug substance and its metabolites should be available to allow intelligent planning of formal pharmacokinetic studies of the drug

in the formulations it will be used during phases 2 and 3. Before beginning phase 2, the sponsor should have sufficient information available to make an informed estimate of the doses and dosing regimens that should be explored during phase 2 controlled experiments.

3.2. Phase 2:

Fundamentally, the goal of phase 2 is to document efficacy and identify the parameters of the treatment regimen (dose, dose interval, induction method, etc.) that are likely to maximize a product's therapeutic ratio in well characterized samples of demented patients. Because of concerns about needlessly exposing patients to ineffective, but pharmacologically active and, therefore, potentially harmful substances, phase 2 studies should patients to test the experimental null hypothesis). This is ordinarily accomplished by controlling sources of variance that tend to obscure modest treatment effects.

Accordingly, phase 2 studies commonly enroll samples of patients that have fewer medical illnesses and are less severely impaired than typical patients with dementia. To further enhance sensitivity, the sample selection process may employ maneuvers to increase the prevalence of patients thought likely to respond to the treatment. For example, in several recent (circa 1990) antedementia drug trials, patients were selected for study because they exhibited, during a pre-randomization phase, an apparently positive response to the investigational drug. While this sort of selection manoeuvre clearly undermines an experiment's external validity, it is a perfectly acceptable strategy in phase 2 where the goal is to demonstrate that the investigational drug has a therapeutic effect in at least some patients.¹¹ In any event, there is ample opportunity to explore dose or plasma response relationships and the moderating effects, if any, of disease severity, stage, and various patient characteristics on the therapeutic response in subsequent clinical trials conducted after "preliminary evidence of efficacy has been gained i.e., in late phase 2, phase 3).

3.3. Phase 3:

Phase 3 is traditionally the period during which a drug of established efficacy undergoes testing under conditions more representative of those which are thought

likely to prevail once it is marketed. As initially conceived, Phase 3 was intended to provide an opportunity to gain experience with the drug in settings more complex than those in Phase 2 investigations, which, as noted above, are often designed primarily to document a drug's efficacy under 'idealized' conditions.

In theory, testing a drug in relatively unstructured clinical settings will enhance the likelihood that risks specifically linked to its use in unique or vulnerable subgroups (e.g., the elderly, the severely ill, those receiving concomitant medications, those with renal or hepatic failure) will be identified prior to marketing. Unfortunately, even fairly large phase 3 studies involving one to two thousand patients are still too small to detect events that may prove to be common in certain subgroups within the population. One reason is that patients belonging to the vulnerable subgroup may simply not be represented in the typical drug development cohort.

In more recent times, in an effort to accelerate the pace of drug development, there is an increasing tendency to merge Phases 2 and 3 of drug development. In particular, it has become common to carry out large multiclinic investigations enrolling hundreds of patients to gather definitive evidence of both safety and efficacy. Indeed, the continued administration of an experimental drug (i.e., so called open extension protocols) to those who were participants in controlled investigations has become an important source of evidence used to document the safety of new drug products.

Unfortunately, this may produce a somewhat biased sample for evaluation, leading to the study of patients who are selected by virtue of their tolerance or preference for the drug. Thus, there is still a need, during Phase 3, to conduct large scale tests with patients who are naive to the product.

4. Design Issues

4.1.1. The need for internal controls:

The demonstration of antidementia efficacy requires a showing of a favorable difference between the investigational agent and an internal (concurrently randomized) control in a validly conducted clinical investigation.

The extent of variation among samples of patients drawn from the population with dementia is far too great to permit the use of non-concurrent (i.e. external) controls. Consequently, each clinical study intended to document the efficacy of an antedementia drug must include an appropriate 'internal , control as a means to determine whether the study's outcome, if nominally positive, can be unambiguously attributed to the effects of treatment with the experimental drug rather than to spontaneous fluctuations in the severity of the manifestations of the dementing process in the particular sample of patients evaluated¹³.

For studies evaluating antedementia treatments, placebo is the preferred choice for an internal control¹⁴; however, a subtherapeutic dose of the investigational drug or some less than optimal therapeutic dose of some other pharmacologically active agent might, provided certain conditions¹⁵ are met, be used instead. Regardless of the type of control employed, evidence of efficacy derives from a showing that patients randomized to the investigational drug fare significantly better than those concurrently randomized to the control.

4.1.2. The value of the fixed treatment level design.

Beyond demonstrating that a product is 'effective,' phase 2 studies should attempt to assess the link between dose (or drug plasma concentration), and dosing regimen (drug plasma level fluctuations) and both therapeutic and untoward responses. Ordinarily, this is best accomplished using study designs that randomize patients to two or more fixed 'levels' of experimental treatment¹⁶. Critically, 'fixed treatment level' designs do not require that patients be randomized to their final, full predetermined dose on the very first dose or day of treatment. Indeed, such a rigid dosing policy can, if a drug has many dose or plasma concentration dependent side effects, cause a fixed treatment level design to fail (patients assigned to the higher dose levels selectively dropout for adverse reactions). In such circumstances if there is any chance that tolerance to dose related side effects will develop, patients assigned to higher treatment levels should be gradually titrated to their predetermined dose or plasma concentration. This strategy is acceptable so long as 1) the levels of treatment (dose or concentration) assigned are specified prior to the experiment, 2) the outcome assessment for each treatment level is made after steady state is achieved and sufficient time has elapsed to allow the full therapeutic response to develop under these

stabilized conditions, and 3) a parallel gradual dosing strategy is employed for those assigned to lower doses or concentrations to avoid inadvertent disclosure of treatment assignment to those responsible for the management of patients to preclude.

Incidentally, in the absence of a standard treatment for dementia, there is no meaningful 'active' control that can be used in studies of experimental antidementia agents.

Importantly, however, even if a drug were approved for use in the treatment of dementia, it would not remove the need for documenting the efficacy of a new antidementia drugs, in clinical trials with established 'assay sensitivity.'¹⁷

Given the foregoing discussion, it is clear that one preferred approach to the assessment of a new antidementia drug would involve the use of a clinical trial design that calls for the randomization of subjects to treatment with placebo and 3 widely separated, fixed¹⁸, dose levels (or plasma concentration ranges) of the drug. This parallel, fixed treatment-level design is not only capable of documenting a drug's efficacy, but it can also provide preliminary information about the relative toxicity and benefits of the various dosing regimens employed in the experiment.

4.1.3. Parallel and cross-over designs:

Ordinarily, parallel designs are considered superior to crossover designs for the study of antidementia treatments. In theory, however, a crossover design may be employed if its treatment periods are relatively short and carry-over effects and/or withdrawal effects associated with the use of the drug are so insignificant that they are unlikely to confound the experiment's interpretation. Unfortunately, the existence of carry-over and withdrawal effects are commonly discovered only after the completion of a study at the time its results are being analyzed. In any case, if a sponsor does conduct a study using a cross-over design, it must be carried out in a manner that will permit its assumptions (i.e., no carry-over, no withdrawal, no treatment by period interactions) to be reliably evaluated from evidence developed in the experiment (i.e., there must be enrollment of sufficient numbers of subjects to provide adequate power to test for the presence of these confounding effects). In particular, the sponsor must document that patients entering any period of the design other than the first have returned to the clinical state they exhibited prior to the start of that first period. If this cannot be

demonstrated, the sponsor will have to explain why the assumptions of the design have not been violated.

Additionally, the sponsor electing to use a cross-over design in any study lasting more than a week or so, must be prepared to defend the suitability of the design for the evaluation of an antideementia drug, especially one that is intended for chronic administration.

Given the issues discussed, the presumed advantage of the crossover design (i.e., a reduction in variance contributed by between subject differences) may not be sufficient to overcome its liabilities.

4.2. *The choice of experimental conditions:*

4.2.1. The inter-relationship between the testing environment and the nature of the patients studied.

A controlled trial of a new drug can be carried out in virtually any setting given appropriate planning and resources. Often, however, especially early in Phase 2, concerns about the potential risks of the drug preclude testing in ambulatory patients living outside a medically supervised environment. The problem ordinarily is not that a drug is known affirmatively to be dangerous, but that the limited experience gained during phase 1 clinical testing cannot provide sufficient reassurance about the drug's safety 'for use,' at least under minimally supervised or unsupervised conditions.

Sponsors are understandably reluctant¹⁹, however, to ask ambulatory demented patients to enter medically supervised environments for the sole purpose of participating in a study. The hardship imposed upon such patients may be somewhat reduced if testing is split between inpatient and ambulatory environments. For example, induction and dose titration can be accomplished within a medically supervised environment. After a period of time judged sufficient to establish steady state plasma concentrations at the maximum dose to be given, patients may be discharged to their usual place of domicile provided that monitoring of treatment continues at frequent intervals.

Ideally, monitoring would include frequent sampling of blood levels of the drug to mitigate any risks associated with accumulation of the drug.²⁰ An alternative strategy is to initiate controlled phase 2 testing of a new anti-dementia drug in more severely impaired-patients who are already institutionalized. Some may fault this approach, arguing that it is more difficult to document drug effects, at least on the core phenomena of dementia, in such advanced patients. On the other hand, even if such studies fail to provide definitive evidence of an antidementia effect, they may provide valuable insights about the nature of the drug's therapeutic action (i.e., positive trends) and insights into the nature of the drug's dose related toxicities. This information may then serve as a basis for the initiation of trials that can be conducted in ambulatory settings with less impaired patients.

In any case, once there is sufficient information to justify the use of the drug in outpatients, studies to evaluate the effects of antidementia drugs can be initiated in patients who are 1) free of concomitant illnesses, 2) taking no or few other active pharmacologic agents, and, critically, 3) still well enough to cooperate fully in the evaluation process which may be quite exhausting for even relatively unimpaired elderly normals.

Clearly, mildly ill patients of the sort just described are not representative of the population of elderly demented patients. However, it is widely believed that mildly ill patients will be more likely to respond to treatment than those with advanced disease²¹. As the primary goal of phase 2 is to establish efficacy, the potential gain in efficiency from using mildly ill patients seems worthwhile even in the face of some loss in the trials external validity.

4.2.2. Subject selection criteria:

4.2.2.(a). Diagnosis

Ordinarily, subjects enrolled in a study intended to document the efficacy of an antidementia drug should meet standard, widely accepted, diagnostic criteria (e.g., DSM-III-R or those of the NINDS/ADRDA)²². However, mere specification of the diagnosis required for entry is not sufficient. Protocols for studies that are intended to serve as sources of 'substantial evidence of efficacy' must specify the actual tests,

criteria, and maneuvers required to meet the inclusion and exclusion diagnostic criteria being employed. For example, it is not sufficient to say that thyroid disease will be excluded by appropriate tests; rather, a specific test or tests, cut score criteria, and test methodology must be specified in the protocol. Moreover, the final study report must provide documentation to show that the findings of the tests required by the protocol did not require the subject's exclusion for thyroid disease.

The point is that there must be adequate documentation for assertions made about the characteristics of patients participating in clinical studies that are to be presented in NDAS. This applies to reports and findings regarding physical examinations, laboratory tests, performance tests, behavioral ratings, etc.

Special efforts should be taken to document that the patients selected do not suffer from a condition that may be confused clinically with dementia. In particular, it is important to document that patients do not suffer from retarded depression (i.e. pseudodementia), delirium, or some primary neurologic or systemic illness that can mimic dementia (e.g. normal pressure hydrocephalus, Parkinson's disease, brain tumor, myxedema, drug-induced deliriform illness, etc.).

4.2.2.(b). Subject classification by stage and severity of illness

The stage and severity of the dementia affecting each subject participating in a clinical trial must be assessed and recorded systematically in a manner that will be readily understood by other workers in the field. In the absence of such information, it is virtually impossible to reach any sort of valid conclusion about a clinical trial's external validity. Knowledge about stage and severity may also affect the chances of replicating successfully the results of a positive study.

Unfortunately, a standard system for describing the severity and stage of dementia has not yet been adopted by those working in the field. Nonetheless, this difficulty notwithstanding, reports of clinical trials acceptable for regulatory purposes must provide 1) an estimate of each patient's stage of dementia on some instrument with clinically understandable anchor points that has gained a reasonable degree of acceptance within the community of experts (e.g., Reisberg's Global Deterioration Scale) and 2) a measure of each subject's performance on some objective comprehensive test of cognitive function. Examples of the latter include the Mini-

Mental Status Exam (MSSE) (Folstein et al. 1975), the Alzheimer's Disease Assessment Scale (ADAS)(Rosen et al., 1984], the Memory Information Test (MIT) (Blessed et al., 1968), and the Dementia Rating Scale (DRS) of Mattis (Coblentz et al., 1973).

Although not a regulatory requirement, the use of the same assessment battery for staging and severity assessment in all major clinical trials of a sponsor's drug development program is encouraged.

As to specific choices, the agency cannot endorse the use of particular instruments. A sponsor would be well advised, however, to choose tests and instruments that have face validity and are viewed as acceptable by a large number of experts working in the field. It is unlikely that any one test or approach will gain the endorsement of all authorities, but it is better to employ a test that has been used widely (i.e. by different investigators) than one which is the 'pet' project of a particular individual or institution.²³

The recommendations offered are in no way intended to discourage the use of non-clinical methodologies for the classification of patients. To the contrary, there is a need to develop independent methods to diagnose and subclassify patients presenting with dementia. Such tests may provide invaluable insights into the nature of the dementing process, and may even lead to the identification of traits or states that predict responsiveness to drug treatment. Importantly, the successful development and validation of such non-clinical methods will require their use in clinical trials.

4.2.2.(c). Ancillary subject characteristics.

It is important to collect and report information about study participants that might affect their response to treatment or the investigator's ability to assess their response. Thus, beyond the routine documentation concerning each subject's stage and severity of illness, it is important to provide information about a subject's use of prescription and non-prescription drugs, level of physical disability (e.g., impairments of hearing and vision, arthritis, etc.), and level of self care immediately preceding entry to the study.

4.3. Dosing issues:

4.3.1. Choosing the dose and dosing regimen to study:

The task of documenting the efficacy of a drug and developing a regimen for its safe administration is best undertaken with basic information about the drug's clinical pharmacology and ADME in hand (i.e., presumably some preliminary data will have been gained during Phase 1 clinical testing). Obviously, if a clinical experiment is to succeed, the experimental drug must be administered in a manner that allows plasma concentrations presumed necessary to produce a therapeutic effect to be achieved without undue degrees of toxicity and/or dysphoric effects. Clearly, knowledge of a drug's metabolism, systemic bioavailability, rate of elimination and the relationship between plasma drug concentrations and dysphoric and/or untoward pharmacologic effects is invaluable in determining how often a drug can and/or must be given.

4.3.2. Enhancing compliance:

Because poor compliance may lead to the loss of a potentially effective antimentia drug, every effort should be made to ensure that subjects and investigators comply fully with the dosing plan for the experiment. While good study protocols mandate routine checks on patient compliance (plasma or urine sampling, pill counts, etc.), it may also be helpful to take steps to enhance compliance before a trial is actually begun.

For example, both product formulations and dosing regimens should be designed with patient compliance in mind. The palatability (i.e., taste, appearance, smell, consistency) of the dosage form should be considered as well as its ease of its administration and consumption. The elderly individual, even if not demented, may be physically impaired to the extent that it becomes difficult for him or her to open a container of drugs. Similarly, visual impairments may make it impossible for many older patients to identify the contents of a container or follow the dosing recommendations written upon them. The timing and complexity of a regimen may also create difficulties, especially for those with emotional and physical impairments.

For these reasons, among others, experts urge that ambulatory patients living outside special care environments not be included in clinical trials unless they live with a

responsible caregiver who agrees to cooperate in the process of drug administration and patient monitoring.

In sum, it behooves those conducting clinical investigations enrolling the impaired elderly to pay careful attention to matters of compliance.

4.4. Efficacy assessment:

4.4.1. Prospective identification of major outcome assessment variables: the avoidance of multiplicity.

The protocol for every clinical study intended to serve as a source of 'substantial' evidence of efficacy should prospectively identify which outcome variables among the many assessed will be employed to evaluate the clinical investigation's overall outcome vis a vis the efficacy of the drug. Prospective designation of outcome variables is necessary to prevent the overall experiment's type I error rate from being grossly inflated over the nominal 'alpha' level at which each outcome variable assessed is tested.

However, this recommendation allows, provided that the designation is made prospectively, regulatory point is that the outcome variables must be specified before the experiment is analyzed, preferably before it is conducted. In no case, should the outcome measures be selected on the basis of an evaluation of the data developed in the study.

4.4.2. Specific assessments required to document an 'Antidementia' claim:

To gain an antidementia indication for a product, a sponsor must provide substantial evidence that the product 1) has a clinically meaningful effect and 2) exerts its effect on the 'core' manifestations of dementia. This compound requirement can be met by showing, in more than one adequate and well controlled clinical investigation, that the drug product is superior to an appropriate control treatment on both 1) a global assessment performed by a skilled clinician and 2) a performance based, objective test instrument providing a comprehensive assessment of cognitive functions. The global assessment ensures that the effects detected are clinically meaningful; the

performance based assessment instrument ensures that the effect of the drug is upon the 'core' phenomena of dementia.

A compound requirement for establishing an antidementia claim is considered necessary to 1) preclude the approval of drug products that produce no clinically meaningful effects on the overall status (e.g., health, function, etc.) of demented patients, but do, because of their pharmacologic activity, cause detectable changes in patient performance on objective tests that are of uncertain clinical relevance, and 2) preclude the award of antidemential indications to drug products that exert a beneficial, but non-specific and/or pseudospecific effect on the overall clinical state of individuals who happen to be demented (e.g., effects on sleep, appetite, etc.).

The decision to use a combination of two different types of outcome assessment to evaluate the efficacy of antidementia drugs was made with the support of a number of experts working in the field of dementia and geriatrics²⁴.

4.4.3. The choice of the performance based comprehensive cognitive assessment instrument:

As noted, a definitive efficacy study intended to support an antidementia claim must employ an instrument that has a documented ability to detect changes in the core cognitive manifestations of dementia. Which instrument is used is not important so long as the one selected yields a performance based assessment. Preferably, the instrument chosen will have been successfully used in clinical studies with demented patients, and will be recognized as valid and reliable by a substantial proportion of experts in the fields of dementia and neuropsychological assessment. Examples of performance based assessments, that may be used include many of those identified as useful for assessing the severity of the dementing process (see Section 4.2.2.2).

The sensitivity of the instrument and the level of pathology it assesses should be matched to the severity of illness exhibited by the patients studied. In the absence of established effective treatments for dementia, the sensitivity of a rating scale to changes in the core phenomena of dementia can so far only be documented through repeated testing of cohorts of demented patients followed longitudinally. In any case, a rating scale selected for use in an efficacy study should ordinarily have been tested and evaluated in patients at several stages of the dementing process. Estimates of the

mean rate of deterioration as measured by the scale (and the variance associated with those estimates) in several samples of typical demented patients can be helpful in estimating the power of planned experiments. For example, for a drug that slows the rate of the dementing process, but does not cause improvement over baseline status, the expected maximum treatment effect is equal to the change in the average score attained on the instrument over an interval of time equal to the duration of the planned study.

4.4.4. Global assessments:

The clinician's global assessment serves as the primary measure of the clinical utility of a product's antidementia effect.

Global assessments offered by clinicians, however, have certain limitations and problems. The subsections that follow discuss the type, choice and use of global assessments ratings that can be made by clinicians.

4.4.4.(a). Types of clinical globals and their general properties:

Two types of clinical global assessments are used commonly in clinical investigations as indicators of the overall status of patients.

One type, the 'clinical global improvement rating,' is designed to capture the extent of overall improvement or deterioration that the clinician perceives has occurred in the patient's status since an earlier evaluation (i.e., usually, a baseline evaluation).

The second type, the "absolute global severity assessment," is intended to capture the absolute severity of the medical condition affecting the patient. The degree of severity is judged in relation to the full range of pathology exhibited by patients suffering from the disease for which the experimental treatment is being evaluated.

Both types of global ratings rely heavily on a rater's clinical skills, training, and prior experience. The facets of patient behavior and appearance considered by a clinician formulating a global assessment are not ordinarily specified; indeed, the rater determines (consciously or unconsciously not only which attributes contribute but determines their relative importance to the assessment offered. Nothing prevents a

rater from focusing on different attributes or assigning different weights to attributes on different occasions.

Global scores, however, are often standardized; commonly, for example, a rater is only allowed a limited number of options for recording an assessment. Thus, the value of global rating might be limited to a fixed, small sequence of integers ordered along a dimension of increasing or decreasing severity/intensity (e.g., a 7 point global improvement scale might use 4 to represent no change, 1 to indicate marked improvement, and 7 to show marked deterioration, etc.)

While the use of a limited set of outcome categories reduces the range of numerical ratings that the clinician can assign to a patient, there is no way, short of practical training, to control how different raters weigh and combine different aspects of the clinical picture in their ratings, or where, along the scale they locate various degrees of improvement or deterioration. Of the two types of globals, the one based on absolute severity of illness can be expected to exhibit greater inter-rater reliability. This is predicted by the nature of the tasks involved in making the two types of global assessment.

4.4.4.(b). Contrasting properties of improvement and severity based global assessments

Absolute global severity ratings require a relatively skilled/trained clinician to assign a patient to a stage of illness ranging from very mild to very severe; however, the skills necessary to classify patients according to stage of illness can probably be taught with relative ease, especially if raters receive sufficient training (e.g., instruction, standard case vignettes, etc.) Training can usually be facilitated by providing examples of patients representative of each absolute severity category.

Global improvement ratings, based as they are upon a perceived degree of change in the clinical status of a patient's condition, pose additional problems, however.

To begin, because an improvement score represents a difference between two evaluations, a global improvement score is only valid if it is provided by a rater who sees the same patient on each and every occasion that a rating is made.

Global improvement assessments pose increased difficulties (relative to global severity assessments) in regard to the precision and consistency in which the value of the global assessment made maps to the size of the perceived clinical effect. The magnitude of the clinical pathology that can be mapped to any global assessment scale can be no greater than that between total well being and the most advanced state of the illness under treatment. When treatment is directed at a potentially totally reversible illness (e.g., depression), the maximum range of and potential change in pathology are identical and so, logically, are the representations of that change on either global severity or global improvement assessments. However, in any condition where the extent of clinical improvement is modest (e.g., as in the treatment of dementia), the range of change in pathology evaluated is considerably smaller than the full range of pathology seen in the illness. As a result, the range of change in pathology mapped on the improvement global is narrow compared to that mapped by the absolute global. Put another way, clinicians asked to make an assessment of global improvement are regularly required to assign a set of ordered integers to a range of clinical change that may be no greater than that corresponding to a difference of one unit on the absolute global. It can be argued that this makes the global improvement potentially more sensitive to small clinical effects. On the other hand, it may make the global improvement far less reliable. The likelihood of lesser reliability is also predicted by the fact that it is exceedingly difficult to train raters in the use of an improvement scale where there is no or minimal opportunity to find examples of patients where improvement has been observed.

4.4.4.(c). Additional caveats concerning the use of globals

Irrespective of type, a number of caveats apply to the use of global assessments.

First, global ratings are only valid if raters are unaware of treatment assignment. Beyond the usual precautions ordinarily taken to avoid 'blind breaking,' special efforts should be made to deny those making global ratings any clue to the nature of the treatment assignment. For example, access to information about untoward clinical responses reported by and/or abnormal laboratory test results obtained on the subjects being assessed should be blocked. If possible, those providing global assessments should be required to base their ratings on video-taped interviews presented in non chronological, permuted sequence.

Next, global assessments are intended to be based on clinical observations made personally by a clinician who has had adequate opportunity to sample the patient's behavior and appearance. In particular, a valid global assessment cannot be based on second hand reports, regardless of the alleged reliability of the primary source (e.g., verbal reports made to the clinician by nursing staff or family.)

4.4.4.(d). The choice of global assessments

Despite their limitations, global assessments are the ultimate test of the clinical utility of a drug's antedementia effects. Consequently, a global assessment is required in every clinical investigation intended to provide substantial evidence of an antedementia drug's efficacy.

The question remains, however, as to which global is to be preferred.

The discussion to this point would seem, on face, to favor the use of the global that captures the absolute severity of pathology observed. There is, however, no consensus on this point. In fact, despite its seeming advantages (e.g., presumed greater interrater reliability, relative ease of learning, etc.) some experts are concerned that absolute severity assessments will regularly fail to detect (i.e. be insensitive to) the modest antedementia effects that can reasonably be expected to be produced by investigational drugs of the type now in development, at least over the relatively short periods (e.g., a few weeks or months) that correspond to the duration of a typical clinical trial. Recall, that if a drug totally stops the progression of dementia, its observed treatment-effect can be no greater than the average change in pathology observed in untreated demented patients over an interval of time equal to the duration of the study. of course, if a study is long enough, an absolute global will be more than adequate to detect between treatment differences in outcome.

In sum, it is not possible at this time to endorse one of the two types of global assessment in preference to the other. Either or both can be used. However, if both are used, the protocol for the study should specify which of the two globals will be considered the primary measure for evaluating the efficacy of the drug (i.e., the global to be used in tandem with the comprehensive performance based cognitive assessment instrument).

4.5. Safety Assessment.

Although the traditional goal of phase 2 is to document the efficacy of a drug, phase 2 clinical trials often provide a large proportion, if not the bulk, of information relevant to the assessment of a drug's safety. In particular, the randomized controlled trials of phase 2 often provide the only source of information that can be used to determine the 'attributable' risk of drug for events seen spontaneously in the population being treated. Thus, comparative safety information collected in phase 2 can be extremely important, if not critical, to the approval decision affecting an antidementia drug.

In general, every participant in a phase 2 study should be evaluated at or immediately before, exposure to drug or control treatment begins. This baseline information is critical to

determining, if an abnormality is detected, whether it is reasonably attributable to exposure to the assigned treatment. Evaluations should then be conducted at reasonable intervals throughout the period of exposure to treatment and during the period immediately following drug discontinuation. The latter period may be the only source of information about withdrawal emergent adverse events.

Ordinarily, every patient should undergo a comprehensive physical and neurological examination and have a battery of laboratory and special tests performed. For example, blood chemistries (electrolytes, liver function tests, etc.), blood counts, differentials, urine analyses, stool for occult blood, and EKGs are the minimum acceptable set of tests that should be performed before, during and after exposure to the investigational agents.

The goal of the assessment is to document that the patient suffered no ill effect during exposure. Should any abnormality occur, additional testing, including obtaining samples of plasma for assay for drug concentration, full follow-up and appropriate medical intervention is essential.

4.6. The required duration of Phase 2 studies:

One of the more vexing questions affecting the development of all drug products involves the duration of the clinical trials that will be accepted as valid sources of

substantial evidence of efficacy. For drugs that are used to treat acute, transient illness, there is not much of a problem; the drug is evaluated for at least as long as it likely to be used to produce its desired effect. For example, an injectable analgesic, intended to be used for one or two days

in most cases, might be evaluated in efficacy studies lasting as long as several days to a week.

Drugs intended for palliation of chronic illness, however, pose an entirely different set of considerations. Ideally, the efficacy of such products ought to be demonstrated over the full interval of their probable duration of use once they are marketed. However, practical considerations have made this goal regularly unattainable. Antidepressants, drugs that are routinely administered for periods of 6 months to 2 years in the management of an episode of depression, for example, are evaluated for efficacy in studies lasting but 4 to 8 weeks.

Understandably, therefore, it is impossible to specify precisely how long a drug product for which an antidementia claim will be sought should be evaluated.

In the abstract, it seems easy to argue the principle that longer studies will be more representative of the actual conditions under which an antidementia drug will be used. Moreover, as noted earlier, if a treatment merely retards the rate of functional deterioration on the 'core' manifestation of dementia, the size of the average treatment effect will be a direct function of the duration of the study. Under such circumstances, a statistically significant effect, on a performance measure or a global might be found after a 6 month long, but not after a 3 month long, study.

However, factors favoring shorter studies must also be considered. Patient recruitment for a very long study may be quite difficult. Patients willing to accept randomization to a less promising treatment for a matter of weeks may balk at participating in an experiment that may prevent their gaining access to an active, albeit only putatively effective, treatment for six months. Moreover, the longer the duration of a study, the smaller the proportion of subjects randomized that are likely to complete the study as planned, an outcome that invariably complicates the study's ultimate analysis.

At the time this manuscript is being written (circa 1990), therefore, it is not possible to make a specific recommendation regarding duration of treatment. It seems unlikely, however, that experts will judge studies of less than 3 months adequate to support an antimentia claim.

5. Phase 3

5.1. Overall goals of Phase 3:

Phase 3 is envisioned as a period of expanded testing during which a product whose efficacy has been established definitively in rigorously controlled phase 2 studies is evaluated under conditions more typical of those likely to prevail once the product is marketed. Phase 3 is intended to confirm efficacy, identify risks, and develop directions for use that include advice for dealing with common adverse consequences associated with the use of the drug. It is during phase 3 that experience is gained with the drug in vulnerable populations, 25 populations that could not ordinarily be identified on theoretical biological or physiological grounds. Phase 3 ordinarily provides the bulk of the evidence upon which the warnings and precautions about the use of the drug are based when it is first marketed. Critically, phase 3 is ordinarily the chief source of the evidence of 'safe passage' that is used to set upper limits for catastrophic risks not seen during the testing of the drug²⁶.

5.2. The scope of Phase 3: numbers of patients

The value of a drug development program increases in direct proportion to the extent and scope of the drug's evaluation. Obviously, the warrant of safety and knowledge about the drug increases with the number of patients studied and with the variation and nature of the conditions under which clinical testing is carried out.

In regard to the absolute size of a development program, it is impossible to state precisely what minimum number of patients must be studied before an NDA for an antimentia drug will be approved²⁷, but, at a minimum, at least a 1000 patients should be exposed for a minimum of several weeks to doses within the range to be recommended in labeling; of these patients, perhaps a third or more (e.g., 300 or so) should have been on doses of the drug at or above the median recommended dose for

a period of 6 months to a year. Importantly, these are minimum estimates and may not suffice if any specific safety problem is identified. In any case, the total drug development cohort includes all patients studied in all drug development phases. Accordingly, therefore, the scope of Phase 3 is affected by the scope and extent of prior phases and the evidence of developed in them.

5.3. Outcome assessment in Phase 3

5.3.1. Routine safety assessments

Although the number and kind of observations made on individual patients in phase 3 is generally less than in phase 2, patients in phase 3 trials should regularly undergo comprehensive medical (including routine blood chemistries, urine analyses, CBCs and EKGs), neurological, and behavioral assessments immediately prior to drug exposure and periodically thereafter throughout the course of their treatment. In addition, other outcome assessments may be required; however, the precise nature of these additional assessments will vary with the purpose of each study.

5.3.2. Pharmacokinetic screening

Phase 3 chronic studies provide an opportunity to collect information that may be useful in identifying causal associations between pharmacokinetic and untoward clinical phenomena. Plasma samples obtained from patients exposed chronically to a new drug may also help identify factors contributing to the variability of a drug's pharmacokinetic performance within the population. Thus, the collection of two or more samples of blood from patients at known times following drug administration who are on stable dosing regimens is encouraged in every phase III trial.

5.3.3. Patient selection

There should be few restrictions on the nature of the patients entering phase 3 clinical trials. In general, any patient, regardless of age, sex, concomitant illness or concomitant drug use, should be admitted to a phase 3 study if treatment with the drug is appropriate and the patient suffers from dementia. Put another way, if a demented patient would be likely to receive treatment with the drug if it were marketed, the patient should be considered appropriate for entry into a phase 3 trial.

Sponsors may tend to resist this recommendation, believing, not irrationally, that untoward events arising spontaneously from such 'high risk' patients will be erroneously attributed to the action of their drug. This is certainly a risk, but it must be taken if a fair estimate of the risks associated with the use of the drug are to be gained.

5.4. Special design issues in Phase 3 Safety studies:

5.4.1. Protecting a drug's reputation: controlled safety assessment studies:

One protection, at least against a false implication that an investigational drug causes common adverse events that, in truth, are arising spontaneously from a high risk population, is to assign such advanced, 'high risk' patients randomly to the new drug and a suitable inactive or minimally active control treatment, the latter providing a means to estimate the spontaneous incidence of adverse events occurring in the population being tested.

A major drawback to this suggestion is the difficulty of finding a control treatment that will be acceptable to patients seeking access to new, presumably promising, investigational agents. So long as legitimate doubt exists about the net value of the investigational agent, there is no moral dilemma involved in asking a patient to accept randomization to a treatment that may be inert or marginally useful and known to be relatively innocuous. Of course, the question remains whether it would be possible to recruit sufficient patients to carry out such a study; clearly, the incentives for a patient with a progressive and irreversible illness to participate in any long term study in which there is a chance of randomization to an ineffective or marginally effective treatment are few, if any, if he or she believes that effective or potentially more effective (compared to the control) treatments exist.

Of course, once an effective treatment²⁸ for dementia is found, long term placebo controlled trials cannot be justified. However, once such a treatment is found, it will be an ideal control for the evaluation of the relative safety, of other new drugs.

This discussion illustrates the importance of obtaining as much valid information as possible from each clinical experiment. For example, if a comparatively large number of patients have been studied in controlled trials during phase 2, the implications of a

high incidence of untoward events observed among 'high risk' patients being followed in phase 3 trials that do not employ a control may not be so critical to a drug's image; that is, there will be at least some evidence to support the argument that the increased incidence of untoward events is a function of the patients studied and not the drug. However, this argument is not entirely persuasive; an interaction between the drug and the 'high risk' status of the phase 3 patients may also account for the increased incidence, a point that will have to be emphasized in product labeling should the drug be approved for marketing.

It is also important to acknowledge that a control group provides few protections against serious and/or catastrophic events that occur spontaneously at low frequencies. For example, if only one or two catastrophic events are observed and each has occurred in a drug exposed patient, the evidence of causal association will be weak, but will, nonetheless, have to be emphasized in product labeling, especially if drug exposure is a reasonably plausible explanation for the event.

5.4.2. Directions for use

Efficacy in sustained use Phase 3 clinical testing provides an opportunity to develop information that will enhance the quality of directions that can be written to guide the prescriber in using a drug prudently and safely.

Although it is not critical to approval, information about the duration of a drug's efficacy in sustained use and the consequences of its withdrawal after chronic administration is always valuable. Accordingly, an uncontrolled study intended to assess the safety of a drug in chronic use may be modified in a manner that provides for a phase during which patients can be withdrawn from treatment and re-randomized to the treatment to which they were originally assigned or a suitable control (e.g., placebo).

If there is no difference in the behavior of the groups created following their rerandomization, questions must obviously be raised about the efficacy of the drug in extended use. On the other hand, if clinical deterioration is seen only in the control group, it is evidence that the drug is exerting some sustained pharmacological action. Importantly, however, it is not safe to assume that the drug is actually exerting a beneficial therapeutic effect; the deterioration observed may only be a sign of

physiologic dependence, the clinical findings merely manifestations of a withdrawal reaction. Clearly, whatever the interpretation, a change in status following blinded withdrawal and rerandomization is information that can help the prescriber in the management of patients, and, therefore, important to describe in labeling.

6. The importance of labeling

Ultimately, the approval of a new drug for marketing rests on a judgment by the review team that the evidence submitted to the NDA documents that the drug is safe 'for use' and 'effective in use,' under the conditions of use recommended in its proposed labeling. Consequently, one useful measure of the comprehensiveness

of a development program is the extent to which the information generated by it will support drafting of product labeling. In general, if a sponsor can draft authoritative labeling as required in 21 CFR 201.57, supporting the statements made in each of the prescribed sections with evidence supporting the statements made in each it is likely that the drug development program is reasonably complete. In contrast, if evidence to support labeling statements is unavailable, if attempts to draft labeling require sanguine assumptions and appeals to biologic plausibility, the drug has almost certainly not been adequately evaluated.

6.1. *Meeting with agency staff*

Guidelines provide only general advice about the development of a drug. Accordingly, sponsors are encouraged to consult agency staff periodically. Meetings are ordinarily arranged at the end of Phase 2 and before the submission of NDAS, and for Subpart E drugs, may be held prior to Phase '2 and before IND submissions. Moreover, regardless of the time at which they arise, important issues affecting a drug's development should be communicated to the FDA. Matters of safety must be communicated rapidly and quickly as dictated by regulation. Matters affecting clinical designs and overall development strategy, however, should also be communicated.

If needed, ad hoc telephone conferences and face to face meetings can be arranged, resources and time permitting

7. Practical advice on filing an IND

Clinical research with investigational New Drugs must be conducted under appropriately authorized Investigational New Drug Applications (INDs). To obtain an IND, the prospective sponsor must submit documentation including a completed form 1571.

In effect, the form 1571 constitutes the sponsor's promise to abide by all rules and regulations pertaining to the use of investigational agents. Detailed instructions about how to file for an IND for the study of an antimentia agent may be obtained by writing to the appropriate Drug Group²⁹. However, the following provide a useful introduction into two preclinical areas that affect a sponsor's ability to initiate clinical testing

7.1. Product Identity, Strength, Purity, controls, and Stability:

Before any clinical study can begin, basic information must be provided to the agency about the drug product that sponsor proposes to administer in clinical studies. An IND is ordinarily granted for a particular formulation of a drug substance. Thus, if a sponsor wishes to use another alternative formulation of the drug substance, he or she must ordinarily seek and gain agency permission for modifying the product before administering it to patients. Thus, it is prudent for sponsors to obtain adequate supplies of a particular formulation from an approved source prior to initiating any studies.

If this precaution is not taken, it may become necessary to suspend a clinical trial if supplies run out and an alternative acceptable supplier for the drug product cannot be found. The sponsor should not assume that an alternative formulation may be substituted willy nilly; a different source of a nominally identical drug product may, in fact, be substantively different. As with other IND requirements, the scope, detail and depth of information and documentation needed about a drug product will vary with the proposed extent and duration of its use and the nature of the formulation being employed. For example, much more information about slow release products may be required than about a lyophilized-powder supplied in a sterile ampule-that is reconstituted with sterile saline prior to injection. The reason, of course, is that the

risks associated with the use of a poor slow release product may be much greater than those involving an immediate release one. In particular, the slow release formulation may 'dose-dump' and cause inadvertent overdose of the patient. Applicants unfamiliar with the basic requirements for the submission of the chemistry portions of an IND should refer to :

7.2. *Preclinical toxicology:*

The preclinical toxicological tests required for an IND are adjusted to reflect the extent, duration and proposed use of the product and the current phase of its development. Ordinarily, far less information is required for initiation of phase 1 than for Phase 3. However, even Phase 1 human studies may not ordinarily take place until there is information about the acute risks of the product in at least two animals species.

In addition to tests intended to document that the drug will not kill within minutes to hours of its administration at doses anywhere close to those that will be administered to humans, acute toxicity testing in two species of animals at doses ranging from 10 to 100 fold that to be administered to man should be conducted to gain some insight into the likely toxicity of the drug and the margin of safety that may be involved.

Ordinarily, toxicity testing is conducted by the same route as that to be used in humans. The extent of toxicity testing required will vary from the minimum just described (used for an injectable that will be given at most for a few doses over a period of a day or two) to a full panoply of tests including 1 year chronic toxicity testing in two species, in-vivo life time carcinogenicity testing in two species and, special

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