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DEVELOPMENT OF SUCCESSFUL PHASE 2
Analgesia Protocols

By David Shoemaker, Ph.D., Jack Modell, M.D. and Ben Vaughn

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Introduction

Once a product has demonstrated an acceptable safety profile in Phase 1 studies, it is time to demonstrate proof of concept in initial Phase 2 studies. Phase 2 is a critical make-or-break phase of product development. Preparation of successful Phase 2 protocols requires the development team to leverage their total understanding of the product development process from preclinical to marketing approval. But more importantly, and particularly for analgesia products, successful protocol development also depends on the team's application of keen scientific and regulatory acumen within the targeted therapeutic area. Unfortunately, companies too often jump to implement inadequately designed proof-of-concept studies with hopes for a "quick win" to gain support for future funding or development, or sometimes simply for lack of appreciation of critical success factors for early-phase clinical studies. This rush causes many potentially successful products to be declared ineffective or unsafe in the graveyard commonly known as Phase 2.

This document emphasizes several key points to consider for Phase 2 analgesia protocol design. The first critical protocol design elements discussed are objectives, clinical endpoints, and proof of concept; these three elements are interrelated, as a successfully met primary objective using established clinical endpoints with regulatory precedent ultimately enables demonstration of proof of concept.

Second, several strategies are presented for determining the dosage (dose and regimen) required to progress into adequate and well-controlled Phase 3 studies that will convince regulatory agencies of the acceptable risk/benefit balance in the intended patient population(s) necessary for approval and reimbursement.

Third, guidelines for optimizing inclusion/exclusion criteria through the course of development are discussed. Careful selection of study entry criteria is important to enhance the likelihood of clinical and regulatory success as well as to pave the way for expanding the Phase 3 study population to fully represent the intended market for the product.

Fourth, a statistical analysis plan that supports the attainment of the pre-specified clinical endpoints is of utmost importance, to maximize the sensitivity and accuracy of signal detection. Beyond simply detecting drug effect, an appropriate statistical analysis will also provide an estimate of the magnitude and time course of effect of the product on the clinical endpoint, which is vitally important in determining the subsequent sample sizes and study designs needed for a successful outcome in Phase 3.

Finally, elements of the Phase 2 study design are discussed that can alert the company to potential results that would require additional Phase 1 studies, beyond single- and ascending-dose pharmacokinetic studies, to be conducted in order to reach the ultimate goal of market approval.

Objectives, Clinical Endpoints, and Proof of Concept

The goal of Phase 2 is to collect sufficient information to design a successful Phase 3 study. Of primary importance is establishing a dosage for your compound that elicits the required degree of clinically significant efficacy, measured with a clinical endpoint acceptable to regulators, while maintaining a tolerable safety profile in a population that gives you the best chance of success without defining your population so specifically that no eventual market exists.

Until 2014, defining a Phase 2 clinical objective for a desired analgesia patient population was a difficult task inasmuch as FDA had not published their guidance for product developers to dissect the regulatory requirements for a given population. Consequently, companies would take their best shot at designing a Phase 2 program only to be told at their End of Phase 2 meeting that the FDA expected them to conduct one or more studies in an additional patient population in order to obtain a broad label claim for analgesia.

Since 2014 when FDA issued a comprehensive guidance entitled ***"Analgesic Indications: Developing Drug and Biological Products,"*** analgesic development has gotten much more straightforward. This guidance explained clearly FDA's expectations for development of products to treat the various acute (e.g., postoperative or acute musculoskeletal pain), chronic (e.g., post-traumatic pain, osteoarthritis, chronic low back pain, spinal cord injury, or diabetic peripheral neuropathy), and breakthrough (e.g., oncology) patient populations in need of analgesia. This information, together with the package inserts for recently approved analgesia medications, and their accompanying summary basis of approvals, is sufficient for a Phase 2 analgesia protocol to be designed with well-defined clinical end-points leading to the optimal chance of demonstrating proof of concept for a given investigational analgesic product.

Dosage Determination

Presumably the results from your Phase 1 program have identified a maximum tolerated dose to use as the upper limit of any dose exploration study in Phase 2. The goal of Phase 2 is to arrive at the effective dosage that provides the optimal desired therapeutic effect while minimizing any untoward effects. This is a relatively straight-forward experimental design for a product that is administered only once. For products that are administered multiple times, this becomes an experiment with two variables, dose and frequency of administration.

FDA's guidance recommends first understanding the single-dose characteristics of your product in development including assessment of pain intensity, time to onset, and time to rescue or re-medication, either in a single-dose study or for the initial dose in a multiple-dose study to treat chronic pain populations. Of course these measures should be conducted in a clinically relevant subject population that approximates the eventual patient population targeted in the marketplace without severely limiting the chance of demonstrating proof of concept. It is also imperative to either select validated instruments to assess the degree of analgesia obtained in these studies or meet with FDA to discuss the development of a novel instrument.

Other findings from the Phase 1 program that may affect dosage include a determination of the effect of food or other concomitant medications on the pharmacokinetics (PK) of your drug. For example, if food greatly affects your product's PK you will need to include a range of doses and/or controls for food intake that ensure subject safety. More importantly, if consistency of food intake cannot be controlled for the target indication (e.g., outpatient dosing, advanced cancer pain, etc.), then you should consider study designs

during the Phase 2 program that allow detection of efficacy or safety differences under different food regimens. Ideally, such work would generate convincing clinical evidence to demonstrate that, despite whatever effects food has on single-dose PK, such effects have no influence on the efficacy or safety of your product at steady state (i.e., after multiple doses, if this is how your product is to be taken).

However, if you find that food affects product efficacy, you may need to consider additional pharmaceutics work to identify an alternate formulation with a lesser food effect. Similar considerations apply to concomitant medications likely to be taken in the indicated population, potential impact of renal or hepatic insufficiency, and possibly other intrinsic or extrinsic factors inherent to the indicated population.

It is essential to interface early with clinical experts in the target indication (key opinion leaders - KOLs) to best understand the needs and practices of the target population, so that these factors can be accounted for in the development program. Note that you need not complete all Phase 1 studies before going to Phase 2. However, you should seek expert input as early as possible, as their insights will be instrumental in helping plan whether and when you study how such intrinsic and extrinsic factors affect your product's scientific, clinical, and commercial promise. Uncovering liabilities as early as possible can be invaluable.

Finally, in this age of patient-centered medicine it is advisable to also conduct a survey of patients suffering from these different types of pain. Patients suffering from the three categories of pain (acute, chronic, and breakthrough) each have their needs and optimal requirements for an effective medication and it is extremely helpful to know these parameters prior to designing your Phase 2 study or studies to optimize the chance for success.

Inclusion/Exclusion Criteria

The purpose of this section is to provide recommendations to clinical teams regarding the formulation of inclusion and exclusion criteria in Phase 2 analgesic clinical studies to enhance the quality of subject selection, to simplify and expedite the enrollment process, and to avoid protocol violations and amendments to protocols.

Key principle:

Deviations from inclusion/exclusion criteria should not be allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria specified in the protocol is essential.

Key points:

Inclusion criteria should contain only those items that define the general (target) population desired for study, and the *exclusion criteria* then shape that population by defining which subsets need to be excluded for other reasons, such as safety.

1. Within limits of known safety coverage, criteria should generally allow inclusion of the broadest representation of the population for intended use, but usually not beyond.

2. For each and every inclusion criterion written, the study team should have justification for why that criterion, exactly as written, is necessary to define the desired study population.

3. Similarly, for every exclusion criterion written, the study team should have justification for why that criterion, exactly as written, is necessary to prevent subjects, who in some cases may otherwise be qualified, from participating in the study.

4. Inclusion and exclusion criteria need to be written as clearly and unambiguously as possible, with considerable forethought into the desirability, necessity, and potential unintended consequences of each criterion and any associated parameters.

5. Care should be taken to write the fewest number of inclusion and exclusion criteria sufficient to describe the population to be studied; duplicative, overlapping, and potentially contradictory criteria should be avoided. Challenge yourself to determine whether all of the inclusion criteria are truly required to define the target population, and all of the exclusion criteria are truly required for safety or other limitations to the target population.

6. Inclusion/exclusion criteria should not be copied indiscriminately from one protocol to the next; rather, criteria should be selected anew for each protocol, though previously written criteria can be used for reference.

7. Think about exclusion criteria in terms of where you want to draw the line between "sensitivity" to detect a condition for which exclusion is desired and false positive (exclusion) rate, recognizing the reciprocal relationship between the two, as described in the following example.

    a. **Example:** If one wanted to be near certain that no subject with even moderate systolic hypertension were included in a study, one could exclude all subjects with a systolic blood pressure > 120 mmHg. While such a criterion would likely exclude nearly all subjects with at least moderate hypertension (i.e., the criterion provides extremely high sensitivity for detecting hypertension), it will also inappropriately exclude a very high percentage of subjects who do not have hypertension. Conversely, if the exclusion criterion were set at a systolic blood pressure of 180 mmHg, a relatively small proportion of all

patients with at least moderate hypertension would be excluded (low sensitivity), but virtually no subjects would be excluded who did not have at least moderate hypertension (extremely low false positive rate). Obviously, the most desirable exclusionary value would fall between these extremes, but no matter where it is set, there will be a trade-off between subjects who are unnecessarily excluded ("false positives") and those who probably should be excluded but do not meet the specified criterion ("false negatives"). The study team must consider this for each criterion selected and decide how best to optimize this inherent trade-off; no absolute or perfect solution to this problem exists.

8. Study teams should diligently review inclusion/exclusion criteria with investigators to help ensure that the protocol-specified details are completely understood and that investigators understand that inclusion and exclusion criteria must not be violated. To aid in understanding the inclusion/exclusion criteria, explanatory footnotes should be considered for any criteria for which the rationale may not be evident.

Some additional points to consider:

Phase of development: Early in development, when limited safety information is known, relatively conservative inclusion/exclusion criteria may be needed to ensure patient safety. However, as the safety profile emerges during the course of Phase 2 testing less restrictive criteria can usually be applied. The gradual relaxation of inclusion/exclusion criteria during progression into later-stage trials permits the acquisition of more "real-world use" safety and efficacy information and helps to define appropriate labeling for the target population.

Target population and individual subject characteristics: It is important to understand the target population and subject characteristics under study with respect to laboratory and testing parameters. Generally healthy subjects, for example, can have physiologic or laboratory values outside of the defined “normal range,” yet still be very healthy. For example, a resting heart rate of 45 bpm in an athlete or runner is not uncommon, while bradycardia in a cardiac patient often signals significant underlying pathology or drug effect. Conversely, laboratory values that would be considered abnormal in healthy populations may be acceptable in particular disease states, such as low hemoglobin in patients with rheumatoid arthritis or diabetic nephropathy (anemia of chronic disease).

For analgesic studies, additional considerations include allowing for expected increases in heart rate, respiratory rate, and blood pressure due to pain; careful consideration of acceptable hepatic transaminase ranges given that chronic pain patients are at relatively high risk of acetaminophen and/or alcohol excess (i.e., a relatively low acceptable upper limit will help exclude more of these patients); and, for studies involving opiate administration, particular attention should be paid to excluding patients at high risk of respiratory compromise (e.g., those with sleep apnea, obesity, underlying pul-monary disease). Additionally, given that subjects entering analgesic studies often have higher than background rates of substance abuse, clear exclusion criteria should be written to exclude at-risk subjects based on thorough clinical evaluation (unless these subjects are the target of study).

In short, exclusionary values/ranges need to be adapted to the population under study. Similar considerations apply if the values/ ranges are meant to exclude a specific medical problem. For example,

in the case of serious cardiac arrhythmia (e.g., ventricular tachy-cardia and not isolated ectopic beats), the exclusion criterion needs to refer specifically to the excluded rhythm (or class of rhythm) and not to something more general like “cardiac dysrhythmia,” which could include several benign rhythm disturbances. The study team – and, as necessary, protocol – need to be able to differentiate between normal physiology that may produce a testing abnormality and a truly pathologic condition worthy of exclusion or special consideration.

Alcohol and drug abuse: Subjects with painful conditions, especially chronic ones, are at relatively high risk for misusing alcohol and/or drugs (including prescription medications), and it is rarely appropriate to include such subjects in early clinical studies. Therefore, a specific exclusion criterion for these subjects is required. However, because such subjects are often unwilling or unable to accurately report alcohol and drug use, despite subject appearances or arguments to the contrary, it is particularly important to perform drug testing – to include all classes of commonly abused drugs/medications – and a blood, breath, or saliva alcohol level. Subjects should be advised ahead of time not to drink alcohol within 8 hours of study screening. Of note, for a subject to have positive body fluid alcohol levels when the last drink was at least 8 hours before the test, the blood alcohol level at the time drinking was stopped would have been well above that generally attained by non-heavy drinkers.

A positive drug or alcohol test should generally *not be repeated* since the incidence of a genuine false positive drug/alcohol result is low, and usually much lower than the likelihood of a subject not being fully honest about substance use. Of course, this is not to say that a false positive test result in the face of honest reporting doesn’t occur, but with no way to definitively rule out the

possibility of surreptitious drug or alcohol use (a repeat test that turns out negative does not indicate that the previous test was a false positive), it is usually better for study integrity to exclude all subjects who test positive – even once – for prohibited substances.

Demographics and "standard labs": Conventional demographics or labs such as age, body mass index (BMI), renal function, etc. should not be routinely included without any consideration. Ask yourself whether you actually need BMI, age, or specific laboratory criteria. Instead, could the criteria be written with regard to co-morbid conditions (e.g., a healthy 80-year-old subject versus a 50-year-old subject in poor condition)? Can a more general criterion be used, such as *"no major illness or debility that in the investigator's opinion prohibits the subject from completing the study?"* The use of more flexible criteria obviously requires assurance that these decisions can be (and, during the course of the study, are) properly made, and that minor errors in judgment are not likely to jeopardize patient safety.

On the other hand, it is also permissible to used fixed ("rigid") exclusion criteria – for example, serum sodium < 130 or > 150, systolic blood pressure < 80 or > 160 – *if* excluding these subjects is clinically justified and the values chosen are intended to be unequiv-ocal; e.g., a subject with a serum sodium of 129 or systolic BP of 161 is always to be excluded. The advantage of using fixed criteria is that it sets absolute standards for subject participation that are not open for opinion or debate, which is often desirable; the disadvantage is that it may unnecessarily exclude some subjects who are not at a particular risk that the criteria are intended to prevent.

Operational issues: Not uncommonly subjects are randomized before investigators receive all information relevant to inclusion

and/or exclusion criteria (e.g., a delayed laboratory result). It is important to consider the practical implications of a delayed testing result, which may be especially common when using distant or non-centralized laboratories. Check-steps should be considered in the programming of the randomization such that randomization cannot occur until allinclusion/exclusion criteria have been entered and noted to be consistent with protocol specifications.

It is also advisable to measure concentrations of investigational product in the subjects' blood or urine at various times during the course of the study. This information enables analysis of safety and efficacy data by drug concentration, which is not only helpful for assessing the extent to which these may be concentration dependent, but also for identifying non-compliant subjects whose data can be excluded from exploratory analyses to assess drug effect only in subjects who actually took the investigational product. Moreover, in trials of potentially abusable drugs, ongoing monitoring of serum or urine drug levels can help identify subjects who may be diverting (selling) study drug rather than taking it. These noncompliant subjects should, of course, be removed from the study.

Statistical Analysis Plan

The goals of the statistical analysis clearly align with the overall goal of Phase 2: to gather sufficient information to enable progression to, and to inform the design of, a robust Phase 3 program. However, a number of issues specific to both Phase 2 and analgesia must be considered.

One key issue in Phase 2 is having an unclouded assessment of the likelihood of success of the program. Without controls in place, one can miscalculate the chances of success. From a statistical perspective, this means clearly predefined primary outcome measures, dose comparisons, and an adequate multiple comparisons adjustment must be incorporated into the analysis plan. For an analgesic study, this can lead to some tough choices in narrowing down the precise patient-reported outcome instruments to be used as the primary clinical endpoint(s), as well as the timing of administration. Instruments specific to the underlying disease are preferable (e.g. Western Ontario and McMaster Universities Arthritis Index [WOMAC] for osteoarthritis); however, other considerations may override this choice. For example, the WOMAC A scale relies on a recall of pain over the last 48 hours, which could be dependent on the activities performed. By comparison, a 50-foot walk visual analogue scale has all subjects perform a uniform challenge, then measures pain following that challenge.

Phase 2 is a balance of investigating the product's therapeutic profile – important for informing Phase 3 study designs and end-points – while also understanding that observed results may be the consequence of random variation. Thus, pre-specification and multiple comparison adjustments put some checks in place to provide unbiased measures of the success of the study. This is not to say that a study that "fails" from a statistical perspective should

always result in abandoning the program, but that a carefully controlled study and robust statistical analysis plan are critical to obtaining theinformation required to accurately assess the likelihood of achieving successful product development.

An issue in analysis of analgesia studies (and other therapeutic areas) is the methodology for handling missing data. At FDA's request, **"The Prevention and Treatment of Missing Data in Clinical Trials"** was published by the National Research Council of the National Academies in 2010; since that time, the Division of Anesthesia, Analgesia, and Addiction Products in particular has insisted on more careful consideration of missing data for adequate and well-controlled Phase 3 studies. Prior to that time, the agency had accepted a number of well-established but sub-optimal methods for imputing missing data, typically utilizing some form of single imputation.

The new recommended methodologies require a much greater understanding of the magnitude of missing data; the mechanisms of missing data for a population and product; whether the data are missing at random; whether all treatment arms are impacted equally for these considerations; and an understanding of which approach will best suit the specific issues observed for a given product. While obtaining a complete picture of all these within a Phase 2 program is next to impossible, prior planning can allow a sponsor to gain sufficient insight to make a persuasive case to the agency when presenting their planned analysis. Since this shift, far too many sponsors have been caught off-guard when receiving agency feedback and wasted valuable meeting time and planning time addressing this issue.

Responder analyses have gained some momentum, but have their own set of drawbacks. Each subject is categorized as a "responder"

based on their pain outcome, with consideration to other factors; for example, subjects with significant rescue medication use (based on a pre-defined criterion) might be categorized as non-responders. This approach also obviates many of the missing data issues since subjects who withdraw for certain reasons (or all reasons) can be considered non-responders without a difficult imputation process. The drawback of this approach is that such analyses typically have lower power, requiring a larger sample size to minimize risk. Common cut points for determining "response" for pain are 30% and 50% reduction of pain from baseline. However, considering all possible cut points via a cumulative distribution function (CDF) can allow a sponsor to gain greater insight as to what defines a responder in their population. Statistical tests on the CDF can yield greater power than a simple dichotomous outcome. Including such analyses in the Phase 2 analysis plan allows one to gauge the feasibility of this approach for an adequate and well-controlled Phase 3 study and can yield strong supporting evidence even if the evidence is not sufficient for approval on its own.

Finally, the importance of a proactive approach cannot be stressed enough. Starting from the target product profile, consider each and every desired label statement and the assessments and analyses that will support these statements in the Phase 3 protocols. For each of these, the Phase 2 study serves to flesh out any unknowns and possible risks. These Phase 2 analyses are a robust test of a sponsor's preparation for their Phase 3 equivalent analyses and will ideally reveal any weaknesses in the planning. By methodically considering each analysis as its Phase 3 parallel for the information the sponsor hopes to obtain, costly gaps can be avoided and the sponsor may enter Phase 3 with far fewer risky unknowns (or at least place quantifiable bounds on the unknowns).

Additional Phase 1 Studies

In the Dosage Determination section above, we discussed how extrinsic or intrinsic factors may affect your product's PK, and how such information can influence Phase 2 study design, dose selection, and maybe even the need to reformulate. Additional Phase 1 studies can help inform your drug development strategy and execution; as noted above, most of these types of studies need not be completed before Phase 2, although some of them can provide important information that may influence the goals of your Phase 2 program, particularly if you have a post-Phase 2, proof-of-concept exit strategy.

For example, if your product is an opioid or otherwise might be subject to abuse, you will eventually need to explore your product's abuse liability, ideally with prospectively designed human abuse-potential studies that include pharmacodynamic endpoints to illuminate the degree to which confirmed drug-seeking individuals report liking your drug for its drug abuse effects. FDA's 2013 guidance on the topic **"Abuse-Deterrent Opioids — Evaluation and Labeling"** is informative for the kinds of clinical and in vitro studies that should be considered, and how results from this work can support different "tiers" of definitive label claims.

On a related note, if your product is intended for oral delivery and you think it can be safely manipulated to facilitate dosing, consider conducting studies to demonstrate the safety and bioequivalence of manipulated versus intact product. For example, you could compare the PK of your product when taken intact versus mixed with applesauce before ingestion. Results from these studies could conceivably affect design of some of your Phase 2 studies, although

more likely, these data will primarily serve to expand your label language for dosing instructions; depending on the target population, increased dosing flexibility can be an important value-add.

Similarly, if your product is a new formulation of an existing drug, you may want to consider head-to-head studies comparing your product to the reference product for various PK or PD end-points (intact or manipulated). Results from such Phase 1 studies can help secure advantageous language for your product label or provide data to convince a partner company of the comparative benefits of your product. If your product is a new chemical entity, additional studies on metabolism will be essential to better understand the potential for drug-drug interactions, the importance of renal or liver function inclusion criteria for your Phase 2 studies, and maybe even the need for additional safety (animal) studies before proceeding with Phase 2. Although key insights on metabolism will come from concurrent in vitro, animal metabolism, and PK work, it may be necessary or desirable to explore certain questions further in Phase 1 clinical studies.

Sometimes, findings from the Phase 2 program will necessitate additional Phase 1 work. For example, perhaps your Phase 1 program didn't enroll women in sufficient numbers, and you find sex-specific safety, PK, or efficacy signals in your Phase 2 studies. Such results would certainly argue for a Phase 1 PK study to better understand sex as an intrinsic factor that may affect your product's PK, metabolism, and/or safety. Alternatively, perhaps a quality of life endpoint or some other patient-reported information in your Phase 2 study suggests something important about how people might prefer to take your product (e.g., never with food, always at night to avoid an unpleasant side effect, etc.); such findings might need prospective exploration in a follow-up Phase 1 study.

Finally, looking beyond Phase 2, FDA will expect you to submit data on the safety and/or efficacy of your product in pediatric populations unless you can provide compelling arguments or data showing your product will not be used in these patients. Such pediatric studies may include Phase 1 PK and safety studies using an appropriate formulation(s) for the pediatric population(s), with the results ideally supporting a bridge to adult efficacy and safety data. Distinct studies should be considered for different pediatric age ranges, and discussions should definitely be initiated by no later than the End-of-Phase 2 meeting with FDA about your Pediatric Study Plan and the potential for waivers and/or deferrals for different age ranges.

Final Considerations for Success

The following are among the most common mistakes in clinical research design that sabotage Phase 2 study success:

Selecting a research hypothesis that is (1) too broad, (2) not easily tested, and/or (3) is not sufficiently meaningful to patients or relevant to health care delivery or outcomes. Respective examples include: 1) choosing an overly broad research hypothesis that attempts to test a vague or nonspecific outcome (e.g., "this drug reduces 'distress'"), testing multiple concepts in a combined outcome measure (e.g., "this drug reduces a, b, c, and d"), or simply attempting to answer too many questions in one study (e.g., assessing dose response before basic proof of concept safety and efficacy data have been obtained); 2) proposing a hypothesis for which there are no accepted valid or adequately sensitive outcome measures; and 3) selecting outcomes that do not reflect clinically meaningful advantages to patients, either in an absolute sense or relative to existing therapies, including the use of surrogate markers when more direct clinical outcome measures are available.

Encumbering the study design with procedures and assessments beyond those necessary to answer the research hypothesis or provide important scientific information. Although the desire to learn as much as possible from one study is understandable, every procedure and assessment carries a cost in terms of patient and investigator burden (and potentially therefore compliance), statistical penalties and integrity, and detraction from, or unintended and unforeseen influence upon, the critical hypotheses to be tested.

Using methodology (study design, outcomes, statistical analysis, comparator groups, etc.) that lacks the sensitivity, specificity, power, discrimination, and/or validity to optimally detect outcomes of interest. Involving statisticians, therapeutic-area experts, and experts in assessing the outcomes of interest very early in development is essential to help overcome this common shortcoming.

Inadequately considering sources of potential bias. Numerous sources of potential bias may occur in clinical studies, including subtle forms of unblinding (e.g., a treatment having pronounced effects – positive or negative – that are difficult to match in the control group or to mask) and subject and investigator reporting bias. This latter problem has particularly plagued studies involving subjective reporting or behavioral outcomes. Although completely eliminating this source of bias is impossible, outcomes reported by the patient that do not require direct involvement of the investigator-for example, patient-reported outcomes and computer-administered interviews and assessments (e.g., via interactive voice response programs) – are often less biased and produce a greater effect size relative to placebo than those that require investigator elicitation (interview), interpretation, and/or recording of responses. Caution is also advised when investigators feel incentivized to qualify subjects for participation, as even slight variations in interpretation or assessment of inclusion/exclusion criteria can introduce significant study bias. Careful investigator training with emphasis on complete protocol adherence and objectivity is essential.

Conclusion

The careful considerations to be given to the choice of protocol objectives, clinical endpoints, dosage determination, inclusion/exclusion criteria, and accompanying statistical considerations in the design of a Phase 2 analgesia protocol have been reviewed. The attempt was to provide a comprehensive interdisciplinary approach to the design of a Phase 2 protocol for an analgesic in the larger context of a development plan for a successful analgesic marketing approval. To this end, perspectives from a variety of different disciplines have been included from individuals with recent experiences designing Phase 2 analgesia protocols that provided meaningful supportive data to successful marketing applications. Careful consideration of the points examined in this article will facilitate the crafting of a Phase 2 analgesia protocol design that, if executed properly, will yield supportive data for a successful development program while also alerting the reader to avoid missteps and pitfalls commonly encountered in clinical development.

About the Authors

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In the past two years, Dr. Shoemaker has contributed to four successful marketing applications and has significant experience interacting with the Division of Anesthetics, Analgesia, and Addiction Products (DAAAP) at FDA and has obtained marketing approval for products in the US, Canada and the EU. He works closely with medical, biostatistics, clinical operations, and regulatory authoring team members to ensure Rho's effort reflects the advantages of his nearly 20 years marketing application experience.

David has over 25 years of experience in research and pharmaceutical development. He has served as a Program Leader or Advisor for multidisciplinary, matrix management program teams and has been involved with products at all stages of the development process. He has extensive experience in the preparation and filing of all types of regulatory submissions including primary responsibility for four BLAs and three NDAs. He has managed or contributed to over a dozen NDAs, BLAs, and MAAs. He has moderated dozens of regulatory authority meetings for all stages of development. His primary areas of expertise include clinical study design and regulatory strategy for development of novel drug and biological products.

Jack Modell, M.D.
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Dr. Modell is a board-certified psychiatrist with 30 years of experience in clinical research, teaching, and patient care including over 10 years of experience in clinical drug development (proof of concept through phase 4), medical affairs, successful NDA filings, medical governance, drug safety, compliance, and management in the pharmaceutical and CRO industries. His specialties and expertise include neuroscience, pharmacology, drug development, clinical research, medical governance, and clinical diagnosis and treatment.

Jack has authored over 50 peer-reviewed publications in addiction medicine, anesthesiology, psychiatry, neurology, and nuclear medicine. He has lead several successful development programs in the neurosciences. Jack is a key opinion leader in the neurosciences, has served on numerous advisory and editorial boards, and is nationally known for leading the first successful development of preventative pharmacotherapy for the depressive episodes of seasonal affective disorder.

Ben Vaughn
Senior Statistical Scientist

Ben Vaughn has over twelve years of experience in clinical research. He has participated in nearly 20 regulatory submissions, coproduced the ISE for two opioid products; and provided statistical consultation, display generation and submission work for four sep-arate products for OA knee pain. Last spring he attended an FDA advisory committee to represent the sponsor for an opioid product. He has authored responses to various FDA queries regarding NDAs, PMAs, IDEs, and SPAs. Additionally, he has represented sponsors in FDA teleconferences and face-to-face meetings for both OA knee pain products and opioid products. His analytic experience includes cross-over studies, survival analysis, non-parametrics, and extensive work with linear and non-linear repeated measure models.