DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 9(7), 1281-1290 (1983)

Clinical Studies of Controlled-Release Medications

by Vincent Karusaitis M.D.
National Center for Drugs and Biologics

I would like to share with you today my perceptions of when, why and what clinical trials need to be done on oral controlled release products prior to their approval. You will note I said my perceptions. The FDA has not established clear guidelines for these products. I believe this is because there has been more variability in the circumstances and the requirements for approval of controlled release products because the requirements have tended to be individualized to the particular circumstances. Thinking at FDA about the requirements for approval of controlled release products has not only evolved over the last 8 to 10 years but at any given point in time, including now, there have been differences of opinion in different divisions of FDA about what the requirements should be. The effect has been to obscure the generic principles that underly the requirements for approval of new dosage forms. These principles and requirements are essentially independent of the delivery system and the route of delivery. It has caused both the industry and the FDA to have difficulty in coming to grips with second generation dosage forms as routinely and with as much consistency as we manage with the dosage form which is first studied and approved. I'd like to emphasize the principles as I see them because I feel they answer most of the questions that are raised and that if we have a

 0363-9045/83/0907-1281$3.50/0

better understanding of them most of our disagreements will disappear.

For completeness sake I would like to briefly point out an important aspect of this subject which has several facets each of which we could spend our allotted time on. My choice of how to spend our time was based on those aspects which I think cause our confusion and not the ones from a scientific, pharmaceutical or medical standpoint which are the most important in deciding for which drugs oral controlled release formulations are desireable and feasible.

The first question which one needs to ask is whether a drug is a candidate for a controlled-release formulation. This is not a trivial question and in fact is a question that needs to be asked, answered and discussed in some depth by chemists, clinical pharmacologists and clinicians as well as marketing people. I don't intend to discuss this today except to say that for the purposes of our discussion I'm going to assume that the answer is yes and that the drug has a short half life, i.e.- its half life is less than 1/2 the usual dosing interval, and that it is a drug that is taken chronically 4-6 times/day.

I think it is worth noting that usually new chemical entities are not initially marketed as oral controlled release formulations. This is not because there are any prohibitions against it, in fact as we get technically more proficient I think we'll see more new chemical entities for oral administration introduced in controlled release dosage forms. The explanation is that you need to know the drug and how it should be used before you can determine what dose or doses for what disease or diseases are suitable for treatment with controlled release

formulations. Again as we get more proficient we will learn how to design and utilize multiple strength controlled release preperations in dosage titration so that we can study them as part of the drug development process and clinicians can start therapy with them more often even with drugs that need careful dosage titration. But in keeping with current norms I'm going to assume for our discussion today that the drug we are discussing is already approved for oral use in an immediately available formulation.

We know of course that we will have to do bioavailability testing. The question is will we have to do clinical studies comparing the efficacy and adverse effects of the new controlled release formulation with the approved formulation. The answer to that generally should be yes and is yes for the hypothetical drug I've described so far. Let me explain. My first slide which is our hypothetical drug shows our expectations. The controlled release formulation not only allows the patient the greater convenience of taking only 1 dose every 12 hours rather than 3, but it smooths out the plasma peaks and valleys. The steady state plasma concentration curves would not look very different than these curves. Mean steady state plasma levels would be the same for both formulations.

Some would argue that if mean steady state plasma levels are calculated to be the same, further clinical testing in terms of relative efficacy and adverse effect incidence are unnecessary. Others would claim that if the peaks and valleys of the immediately available form are within the observed range of steady state blood levels in successfully treated patients i.e.- those obtaining the desired treatment effect without side effects, comparative clinical testing is not necessary. They

would reserve comparative clinical trials for those drugs for which it had been demonstrated that there was a correlation between a narrow range of blood levels and either effectiveness or some adverse effect. In my opinion both of these approaches are based on false assumptions.

The view that steady state is an equilibrium between input and output may be convenient mathematically but in my opinion it is unphysiological and usually not appropriate. It views steady state as a tub with water (drug) flowing in and out and the level staying constant (at drug receptor sites). I view steady state like the tides with the drug coming in (to receptor sites as well as the plasma) and then receding after each dose. For drugs with longer half lifes as is illustrated in the next slide the peaks and valleys at steady state are proportionally smaller and the tub equilibrium model may be appropriate. A drug with a 12 hour half life as depicted in this slide should not require every 6 hour dosing, however. If clinical experience has shown a 6 hour dosing interval to be necessary or beneficial in any way then I think comparative clinical trials should be done to see what further flattening out of the "tides" might do. If a 6 hour dosing interval has not been shown to be necessary or useful I don't see any necessity for a 12 hour controlled release formulation. For many drugs with half lives longer then 24 hours once a day dosing is based on convenience and compliance rather than therapeutic necessity. For such drugs controlled release dosage forms are also inappropriate in my opinion.

What about the argument that in the case of many or even most drugs there has been no correlation between plasma levels and therapeutic or adverse effects and therefore the plasma levels don't mean anything particularly when the peaks and

valleys are within the observed therapeutic range for the drug. I'm not persuaded by this argument because I don't think its based on adequate data. Usually drugs aren't studied and patients aren't followed in everyday practice in ways that facilitate discovering anything except the grossest effects. When asked for data that there are significant differences in therapeutic or adverse effects based on the flow and ebb of the dosing tide, a fair question, I must admit that I don't have very much or very good clinical data either. The most well accepted and unequivocal example is probably the differences between prednisone given as a single dose every other morning versus giving the same dose divided into 1/8 of the total every 6 hours. In those conditions where single dose efficacy and adverse effects can be studied, such as in analgesic testing, there is clearly a temporal relation between effects and the dosage tide. But even with these drugs there have not been many attempts to study in the same way the time course of effects over dosage intervals during chronic dosing. There are also animal data showing significant differences associated with dose timing that suggest we could reap some benefits clinically if we learned more about pharmacodynamics during chronic dosing in man.

But what really persuades me is how much room I see there is for improving efficacy and reducing side effects in the drugs that come through the IND/NDA process. Significant numbers of patients are poorly benefitted and another smaller group has side effects that limit the usefulness of the drug. We drop those patients out or accept their "failure" for either reason as givens without ever attempting to learn anything from their experience. When I talk like this an argument I frequently hear is that practitioners will find these things out "in the real world" as they will have to do anyhow because somehow the real world is different than the IND/NDA process. I don't really know

how much improvement we can introduce by better control over the drug tides but clearly if we don't try to study it we may never know because as I see "the real world" fewer advances in our knowledge about clinical medicine are coming from the practitioner today and more are coming from formal studies. But that is another subject.

I'd like to turn now to the kinds of studies I think we need to do. They should be positively controlled double blind trials comparing the new dosage form to the approved formulation. In the case of new chemical entities, the control formulation should be the one which was used to initially demonstrate efficacy and side effects. I'm assuming the formulations will look different so that a placebo for each will be necessary. Our main concern statistically will be the power of the study to detect significant differences. We will need to make some crucial assumptions about response rates and side effect rates and their variability before the study. We'll also need to decide how big a difference is "clinically significant". If a study shows no difference but fails to pass our predetermined minimum power requirements it should be declared a flop just as we would do in the case of a placebo controlled study if we could show no difference between our test drug and placebo at the P<.05 level. I believe our power requirements for these studies should be at the 95% level. We should not be content with being wrong any more often when our goal is to show no difference than when we try to show a difference.

We should try to look for differences in effectiveness and side effects related to time during the dosage period which we have tended to ignore in the past. The peaks and valleys may give us dosage interval cycles. We should recognize that these

cycles will not necessarily occur at the same time as the plasma peaks and valleys or at the same time in relationship to one another. The compartments where the drug receptors are may have high and low tides at different times just as occurs with the ocean tides in our tidal bays and rivers. It will be important to design studies to look for these offsets and not miss them by focusing on the plasma profile. Actually I think when we look we'll find cycles for many drugs.

When I talk about positively controlled trials and power like this the first question that gets asked is how many patients are required for such studies. The key to this is the size of the difference you want to be 95% sure you could have detected and didn't and the patient to patient variability in the response variables. In the case of efficacy with primary anti-inflammatory study variables we've been looking for a 25% to 50% difference in responses between the different formulations. In side effect variables we've been looking for 5 fold differences in reactions occurring in the 1-3% range, 3 fold differences in reactions occurring at the 3-9% range and 2 fold differences in reactions occurring more frequently then 10%. The bottom line is about 50 to 75 patients in each treatment group in a multicenter study.

This is not a very large number of patients viewed from the perspective of the requirement of 1000 to 2000 patients to establish efficacy and the incidence of adverse effects for new drug entities. Viewed, however, from the perspective of sponsors thinking in terms of 24 normal subjects in a crossover bioequivalency study it represents a considerable increase in the requirements without any additional benefits. This brings us to another controversial area. What do you do with the results of

these comparative studies between dosage forms? Its clear the FDA is not going to allow labeling or promotional claims of clinical superiority based on smoothing out the peaks and valleys without clinical evidence that it makes a difference. Whether that evidence will be one adequate and well controlled study for advertising purposes and two such studies for labeling claims is not completely clear. I think good science and good regulation says that there should be one standard for both which is that there should be two studies.

Good medicine depends on using drugs appropriately. Physicians who are well acquainted with a drug may substitute a new dosage form of it with less attention to the fine print in the labeling or in the advertising than they would give to a drug that is a new chemical entity with which they are unfamiliar. Therefore I believe that those of us with medical and scientific responsibility need to scrutinize the labeling and advertising of new dosage forms more carefully than usual to insure that in their zeal our advertising colleagues do not leave physicians with impressions that cause them to misuse either the new or old dosage form. The next slide shows an example of an ad that I believe has just that potential. This is an ad for a 12 hour sustained release formulation of indomethacin. This formulation releases 25 mg of indomethacin immediately and the other 50 mg over 8-12 hours. In a clinical study of patients with osteoarthritis the sponsor found no difference between this formulation and 25mg capsules of indomethacin given three times per day. They put those 2 facts together and came up with an advertising campaign for a once a day sustained release capsule which gives 24 hours of relief. Now if you look carefully the fact that absorption is for 12 hour and that this has only been demonstrated in some patients with osteoarthritis is in the ad.

But the big print and the big message is "once a day sustained release". I believe it would take an unusally sophisticated physician to figure out the pharmacokinetics and/or pharmacodynamics of the dosage form from this ad. Furthermore I believe it will confuse many physicians who are trying to learn how to use drugs which are given once a day because of long half lives. Although such ads may do well in the short run, I don't believe they are is in the best interest of patients, physicians or a company in the long haul because if physicians don't use a particular formulation properly and get poor results they will quit using it.

Clearly a system that produces evidence of clinically useful differences between dosage forms and allows sponsors to promote such differences is in the best interest of most everyone involved, i.e.- patient, physician and innovator of the dosage form with the advantage. It offers no advantages or for that matter disadvantages to sponsors who manufacture generic products as long as they can do bioequivalency testing to establish "me-too-ness" with the dosage form with an advantage. It does create an additional area for confrontation between FDA and companies who like to promote beyond their data. These sponsors consistently try to suggest that their products have advantages over others based on computer modeling, in vitro, animal or blood level data or even some theoretical basis. Thats another subject though and its only relevance here is that it will get interjected as an argument by people who believe "the American way" or "the free enterprise" system is better and more rightly characterized by current OTC advertising rather than current prescription drug advertising.

I'm afraid I've left you with more problems than solutions. I hope though that I've given you a clear answer to the question

of what kind of clinical studies should be done if they are going to be done and given you some basis for considering when and why you should elect or be required or perhaps even want to do such studies.