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TALKING POINTS

Some Observations on Current and Possible Future Developments in Bioequivalency Testing

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ABSTRACT

Present trends in the evolution of the design and interpretations of bioequivalency studies are reviewed. It is suggested that, although such tests are now being increasingly regarded as clinical mirrors rather than simply quality control tests for final product testing, there is still the possibility of simplifying such procedures. However, care must be exercised to ensure that changes in bioequivalency tests are introduced only after careful public discussions, which should involve both regulators and pharmaceutical scientists from academia and industry. Further, it is important that bioequivalency standards shall be internally consistent and applied in a politically neutral manner.

The present author on several occasions has published his views on bioequivalency tests (1–4). He has advanced the view that bioequivalency tests should be kept as simple as possible, and that, in essence, such tests should be regarded as quality control tests, the functions of which should be to quantify the in vivo release of drug from drug delivery systems (2). In other words, such tests simply should quantify the average rate and extent of input into the human body. In particular, I have argued against the idea of trying to use such tests as ''clinical mirrors'' (2). However, during the past 5 years there has, in fact, been an impressive movement toward a broadening of the concept of bioequivalency. These tests are now generally regarded more as clinical mirrors than just quality control tests, which are only performed in human subjects because of our lack of success in discovering that pharmaceutical ''philosopher's stone,'' a universal equation that reliably links some in vitro test result (such as that determined using a flow-through dissolution cell) to average human blood concentration time profiles.

In fact, bioequivalency tests are now becoming generally recognized as mechanisms for providing sound assurance that bioequivalence not only obtains as an average value in a population, but also exists for individuals in the population. Thus, recently there has been considerable discussion about how to quantify and regulate intersubject variability in bioequivalency studies. Obviously, to quantify intersubject variability, we do need

studies in human subjects. Thus, even if we were now able to determine a reliable in vitro predictor of average bioequivalency, we would presumably still need to perform some in vivo studies to quantify intersubject variance. We now expect bioequivalency studies to provide reliable test data that will allow us to conclude, with a high degree of confidence, that both qualitatively and quantitatively all patients—not just the average individual—will obtain essentially the same concentration/time profiles of drug (and, if appropriate, active metabolites) with either the generic or innovator product.

Also, of considerable interest to students of bioequivalency testing has been the emergence of great interest in the idea of relating the limits for acceptable variance in bioequivalency limits to the pharmacokinetic and pharmacodynamic properties of individual drugs. For example, it has been proposed that so-called narrow therapeutic index drugs should have tighter bioequivalency limits than other drugs. (As Tozer has correctly pointed out, this terminology is an affront to lovers of the English language; a much better term would be narrow therapeutic range [NTR] drugs.) The subject of NTR drugs is, at the time of writing, still unresolved. However, it does seem highly probable that, in the future, the ''one size fits all'' for bioequivalency limits for all drugs will increasingly become unacceptable in many jurisdictions.

The evolution of bioequivalency studies would probably be much more efficient and far less painful if this topic were not at the cusp of powerful and competing financial interests. Thus, to protect their large sales, certain innovator companies have (in the opinion of at least some pharmaceutical scientists) on occasion misapplied science and used unseemly and distasteful political and legal methods to block the introduction of perfectly satisfactory generic products (5,6). On the other hand, there may well be generic companies that, in their desire to exploit a profitable market as rapidly as possible, pay insufficient attention to reasonable scientific and clinical aspects of the design of bioequivalency studies.

As indicated above, our concepts as to how best to design and interpret bioequivalency studies have evolved during the last 15 years or so, and there is no reason to believe that this process of development is yet complete. We may expect further modification of our procedures. Since no one scientist or group of scientists is infallible, it is important that there should be public discussion of potential developments in policies and procedures concerning bioequivalency testing before such changes are implemented. There are opportunities for the FDA to foster public discussion of such issues. The agency is to be commended for allowing pharmaceutical scientists to testify in 1997 before its Pharmaceutical Sciences Advisory Committee on bioequivalency standards for NTR drugs such as warfarin. Also, the agency was a cosponsor with AAPS and the USP of the conference held in Crystal City in the spring of 1998 on NTR drugs. In addition, persons from the FDA spoke at the November 1998 symposium on NTR drugs held at the San Francisco AAPS meeting (4).

THE OBJECTIVE OF BIOEQUIVALENCY TESTS

It is submitted that the objective of bioequivalency testing should be to provide laboratory data that will readily allow a reliable conclusion to be reached as to whether the two products being tested provide essentially the same plasma concentration/time profiles for the parent drug and any metabolite that makes a substantial contribution to therapeutic or toxic effects. It seems possible that the topic of when to require quantification of drug metabolites may become a subject of lively debate in the near future. It is hoped that the FDA (acting in concert, perhaps, as it has on previous occasions, with the USP and AAPS) will sponsor public meetings at which this topic can be fully explored. Because of the intense pressures caused by financial concerns that impinge on bioequivalency test decisions, it is particularly important that this period of public discussion should come before any agency change in policy is made with respect to either individual drugs or classes of drugs.

Bioequivalency tests should be kept as simple as possible. The more parameters that we add to such tests, the more likely it is that we will erect insurmountable barriers for any generic product. The conjugated estrogen story provides a cautionary tale that testifies to the need to avoid excessive, unjustified test requirements.

QUANTIFICATION OF METABOLITES IN BIOEQUIVALENCY TESTS

Although there may be sound arguments in some cases, based on sensitivity or precision factors, for quantifying a metabolite rather than the parent drug (7), our natural preference has been, and should continue to be, normally to base many bioequivalency determinations simply on quantification of the parent drug. Under some circumstances, however, it may well be essential to include quantification of an active metabolite (or metabolites) in a bioequivalency test if the objective given above is to be reached. Traditionally, the FDA has required the

quantification of all active metabolites in bioequivalency studies (8). However, even now that we accept the idea that bioequivalency studies should be clinical mirrors rather than simply final product quality control tests, there may well be some well-defined circumstances that should be considered by pharmaceutical scientists and regulators for possible exclusion of active metabolite quantification. After appropriate public discussion, it may well be reasonable to change our present requirements.

What are the circumstances for which it may be acceptable to consider removing a requirement that active metabolites be quantified in bioequivalency studies? It is proposed that, if the following requirements are met, such action may well be justified:

1. The active metabolite(s) concentration time profile is, at all time points, less than, say, 10% of the comparable value of the parent drug.
2. The type of pharmacologic or toxic responses produced by the parent drug and active metabolite are substantially similar.
3. It has been clearly established that all the pharmacokinetic processes that govern plasma concentration of the parent drug and active metabolite are linear at all plasma concentrations likely to occur when the drug is used clinically.
4. The drug delivery system is not designed to be an extended-release product.

On the other hand, there are situations when it is not possible to justify the elimination of quantification of active metabolites if indeed we wish to make a decision on bioequivalency that is reliably grounded on hard quantitative data.

Probably an extreme example of when it is not appropriate to dispense with quantification of an active metabolite would be provided by the following scenario. The innovator's drug product is designed as an extended-release drug delivery system with a dosing frequency reduced from that used for an immediate-release system. The literature on the drug substance does not allow us to conclude that absence of nonlinearity in its pharmacokinetics has been proved. The mechanism of release control in the innovator's product is significantly different from that used in the generic product. At steady state, the concentrations of active metabolite are approximately equal to the concentrations of parent drug. There are significant differences in the nature of the pharmacologic response produced by the parent drug and the active metabolite.

It might be argued that, even in the above extreme case, it would be possible to rely on only single-dose studies of the parent drug and not require steady-state studies involving quantification of parent drug and active metabolite. Such a thesis is only tenable if we are prepared to break entirely with a tradition of requiring objective, scientific laboratory data and instead rely on an intellectual edifice of clever conjecture that depends on mighty massaging of data and extensive extrapolation. Such a process is fraught with hazard and cannot provide quantitative confidence levels of the estimate of bioequivalence that can be obtained from hard experimental results.

Suppose that, in the above example, a single-dose bioequivalency study of the parent drug showed that the generic product was characterized by pharmacokinetic parameters for both rate and extent of absorption that are within 20% of the innovator's product. It might be argued that if we know that the extent and rate of input of parent drug into a patient's vascular system for a single dose is similar for an innovator and generic product, then there is no cause for concern about the possibility of there being substantial and possibly clinically significant differences in the plasma concentrations of either the parent drug or active metabolite at steady state. Such an argument is fundamentally flawed unless it has been proved that the pharmacokinetic parameters are linear and that the extent and rates of absorption are identical, not just similar. If a single-dose study of the parent drug demonstrates bioequivalency for the measured parent species, there can still be statistically significant differences in extent or rate absorption as long as the average and 90% confidence levels are within the 80% to 125% limits (for log transformed data). Thus, it is quite possible, for example, that the rates of absorption of the two products could differ, say by 5%. If, at steady state, nonlinearity occurs in the pharmacokinetics, this relatively small difference in rate of input of parent drug could be magnified so that the differences in the concentrations of the parent drug or active metabolite could be substantially different at steady state. Clearly, the possibility of one or another species showing significant differences in accumulation cannot be ruled out. Further, if there is a difference, at steady state, in the relative concentrations of parent drug and active metabolite, then there will be a difference in the therapeutic or toxicologic spectrums between the innovator's product and the generic product. Such a situation obviously points away from a reliable conclusion of bioequivalency. In this type of case, therefore, there can be no substitute for direct quantification of both parent drug and active metabolite at steady state.

CONCLUSION

Policies and procedures concerning the determination of bioequivalency have evolved in recent years and will probably continue to develop. It is essential that, before changes in this area are implemented, there should be adequate opportunity for public debate by interested parties. Changes in policies should not be made on an ad hoc basis or made as a result of consideration of any one drug product without public discussion.

There does appear to be a strong case for removing the necessity of quantifying all active metabolites in bioequivalency studies. In some carefully defined situations, it may well be appropriate to relax such requirements. However, in other situations, such a change is quite unwarranted, and quantification of the active metabolite should remain as an essential element of any bioequivalency study.

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