MEMORANDUM

DATE:	June 22, 2000
TO:	Advisory Committee Members and Guests
FROM:	Alternate Dosing Regimens Working Group Division of Antiviral Drug Products
THROUGH:	Heidi Jolson, M.D., M.P.H. Director Division of Antiviral Drug Products
SUBJECT:	Background Package for July 25, 2000 Advisory Committee

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Introduction

On July 25, 2000, the committee will be asked to consider issues pertaining to the role of pharmacokinetic data in the evaluation of new formulations, alternate dosing regimens, and new dosing combinations of approved antiretroviral drugs. Because of recent interest in the development of extended release formulations and simplified dosing regimens, including regimens utilizing pharmacologic enhancement via metabolic inhibition (e.g., low dose ritonavir), the division believes there is a pressing need for an open discussion of issues relating to this aspect of antiretroviral development.

Approval of New Molecular Entities

Accelerated and traditional approval for new antiretroviral agents are typically based on two adequate and well –controlled trials that demonstrate a particular drug's contribution toward short term reductions in HIV RNA (e.g. 24 weeks) and sustained suppression of plasma HIV RNA levels (e.g. $\geq$ 48 weeks), respectively. For various reasons a sponsor may chose to either simplify the approved dosing regimen or manufacture new formulations post approval. New formulations of approved antiretroviral drugs can be based on pharmacokinetic (PK) data providing the new formulation is bioequivalent to the approved formulation; whereas PK, efficacy and safety data have been required to support approval of alternative dosing regimens and new formulations with different PK profiles. Issues relating to the type and amount of data needed in the evaluation of alternative dosing regimens and new formulations for approved antiretroviral drugs will be highlighted throughout this document.

Overview of the Issues Pertaining to PK/PD Relationships for Antiretrovirals

Given the large number of potential drug regimens and antiretroviral dosing combinations, the division acknowledges the need to appropriately streamline the amount

of data required to support the marketing of new regimens/formulations of approved drugs. Pharmacokinetic (PK) data could potentially be utilized to increase the efficiency of the clinical evaluation of alternate dosing regimens. However, to use PK data appropriately, relationships between pharmacokinetic parameters of antiretroviral drugs and pharmacodynamics (PD), i.e., changes in HIV RNA, need to be well defined. During this advisory committee meeting we will summarize studies that have attempted to characterize relationships between various PK parameters and virologic response or safety outcomes. We will additionally discuss limitations of currently available data and discuss future research needs.

Although some studies have shown interesting correlations between various PK parameters and virologic outcome for certain drugs, the current compilation of data has many limitations. For example, for the nucleoside reverse transcriptase inhibitors (NRTI), relying on plasma concentrations may not be appropriate because drugs of this class require intracellular phosphorylation to exert an antiviral effect. To date, assays measuring the intracellular concentrations of phosphorylated NRTI have demonstrated variable reliability. Consequently, we will focus the advisory committee discussions primarily on drugs (PI and NNRTI) for which plasma concentrations are considered to be most relevant.

Other limitations of available data relating PK and virologic outcome include small sample size and the presence of confounding clinical factors such as protein binding, the degree of adherence, the impact of resistance, or the effect of other drugs as part of combination regimens. Furthermore, investigators have not uniformly analyzed virologic outcome, thus hampering the synthesis of relationships between PK and virologic outcome across studies. For example, in the available literature and abstracts virologic response has been analyzed using initial slope, change from baseline at times ranging from 7 days to 24 weeks, or by assessing the proportion of patients with HIV RNA levels below an assay limit at one of several time points. Finally, typical study designs result in a high degree of correlation between the various PK parameters. All of these factors have contributed toward a seemingly confusing collection of studies; consequently, there is substantial controversy regarding which particular PK parameter(s) may be most predictive of virologic response for any drug class.

Based on the scientific principle that maintaining plasma concentrations above a threshold necessary to inhibit viral replication (e.g., in vitro IC_{50} or IC_{90} corrected for protein binding) throughout an entire dosing interval is essential, many investigators embrace the concept that the minimum plasma concentration (C_{min}) is the most important parameter for predicting virologic success. This concept is rooted in what is known about the viral kinetics of HIV, which predict that suboptimal concentrations of antiretrovirals could result in the production of large numbers of virions (perhaps in the order of 10^9) under conditions of high selective pressure. This situation would be expected to put patients at risk of eventual virologic failure due to the emergence of mutant HIV strains. Although the concept that C_{min} is the most important PK parameter is highly plausible, clinical data have not confirmed this. In addition, there are several practical problems that must be addressed before applying this concept to the clinical

situation. First, defining the appropriate minimum threshold concentration for each antiretroviral is a difficult task. Predictions based on in vitro inhibitory concentrations may not be sufficient for clinical situations, particularly for treatment experienced individuals with varying degrees of viral susceptibility. The measurement of in vitro inhibitory concentrations is highly variable, depending on the viral strain, the cell culture studied, and the methods for determining the impact of protein binding. Second, it is often difficult to measure the actual minimum plasma concentration in the clinic, due to factors such as adherence, variability in the timing of dosing and blood sampling, and pharmacokinetic variability. Also, plasma concentrations of some drugs may continue to decline from pre-dose levels for a short time after ingestion of the next dose as a consequence of delayed absorption.

In addition to determining which PK parameter might best predict virologic response, it is equally important to consider how changes in PK might adversely or favorably affect the safety or tolerability profile of an antiretroviral. Some have proposed that C_{max} is the parameter of most relevance to drug tolerability. However, some studies have shown that AUC or average concentrations may also correlate with toxicities. It seems likely that not all adverse events will correlate similarly with one particular PK parameter.

Despite the limitations of the current scientific knowledge of PK/PD for antiretrovirals, HIV therapeutics have accelerated rapidly in the direction of simplifying dosing regimens while attempting to improve a drug or regimen's therapeutic index. It is clear that the regimens used in clinical practice are diverging from those recommended in product labeling. Since the division recognizes the need for regimens that offer advantages for adherence or therapeutic effect, we are anxious to obtain the committee's feedback on how the use of PK/PD might enhance and expedite a sponsor's development of alternate dosing regimens. A systematic approach to these issues may help decrease the growing divide between what has been adequately studied and labeled and what is commonly practiced.

In the remainder of this background document, we will summarize the division's/agency's current recommendations for approval of new formulations or regimens, outline some issues regarding the labeling of drug interactions, and provide an overview of the agenda and discussion points for the meeting on July 25.

Current Recommendations for Developing New Formulations of Approved Drugs

A new formulation that meets the standards of bioequivalence relative to a formulation with acceptable safety and efficacy may be approved for marketing. For two products to be bioequivalent, the active drug substance in the new product (test) should exhibit the same rate and extent of absorption as the previous product (reference). The investigator determines the 90% confidence intervals for the test vs. reference ratio of both Cmax and AUC. Using log transformed data, the 90% confidence intervals for the ratios (expressed as percentages) should fall between 80% and 125%.

At the division's discretion, new products that fall outside of the bioequivalence criteria may be approved based on PK, if previous data indicate that the observed differences in

PK are clinically irrelevant. For example suppose that a new formulation met the bioequivalence criteria for AUC, but for C_{max} the 90% confidence interval was 92% to 129%. In such a situation this new formulation may be approved without additional data, if the drug product had previously demonstrated a wide safety margin or had demonstrated safety in clinical trials at higher doses or exposures.

However, in some cases the difference between the established and new formulations may be larger. For example, the lower confidence bound may be 65% for both AUC and Cmax. In the absence of data demonstrating that decreased concentrations provide acceptable efficacy, the division has requested that sponsors evaluate the new drug product in a controlled study for virologic outcome and safety (see the discussion below under "Safety and Efficacy Studies for Approval of New Formulations or Dosing Regimens When PK Profiles Differ").

There also may be cases where a change in formulation may result in an increase in all PK parameters. In this case additional safety data may be required to ensure that the increased concentrations are not associated with additional risks or an objectionable tolerability profile. In the saquinavir example, the sponsor sought approval of a new formulation (Fortovase) with increased bioavailability compared to the approved formulation (Invirase). In addition the new formulation was to be dosed at a higher daily dose, 3600 mg/day instead of 1800 mg/day. These changes resulted in an AUC and C_{max} that were approximately 8 and 10 fold greater, respectively, for the Fortovase regimen compared to the Invirase regimen. For the approval, the division required a study showing superior efficacy of Fortovase compared to Invirase and an additional safety database to support the higher saquinavir concentrations. Approximately 500 patients were followed for 16-24 weeks, a safety database similar to that required for new molecular entities. However there may be cases where the amount and duration of safety information required may vary depending on the clinical significance of the increases in concentrations for the new formulation or regimen. This issue will be addressed in the questions to the committee.

Current Recommendations for Developing Alternate Dosing Recommendations

When evaluating new dosing regimens (tid to bid or bid to qd) sponsors attempt to demonstrate that the new regimen provides comparable plasma drug exposure to the approved regimen. The sponsor may apply the principles of bioequivalence to compare plasma drug exposure between the regimens. However, although a sponsor may demonstrate that AUC over 24 hours is similar for the two regimens, C_{max} and/or C_{min} often differ substantially. In most cases, administering the same or similar total daily dose less frequently results in a higher C_{max} and a lower C_{min}. As with new formulations, when the approval of alternate dosing regimens of approved antiretroviral drugs cannot be based on PK data the division has requested that sponsors evaluate the new regimen in a controlled study for both safety and virologic outcome.

Safety and Efficacy Studies for Approval of New Formulations or Dosing Regimens when PK Profiles Differ

The Division recommends that the new formulation or dosing regimen should be compared to a control regimen (usually the approved dose or formulation) in the context of appropriate combination therapy. Since differences between potent combination regimens may not be evident after only a short course of treatment, the division has recommended that a study be continued for a minimum of 48-weeks. An interim analysis performed after the last patient enrolled has had the opportunity to receive 24 weeks of therapy may be submitted in support of the new formulation or dosing regimen. However, the 24 week analysis would be considered supportive of an approval only if the alternate dosing regimen or formulation showed either superiority or convincing evidence of comparability for both safety and efficacy to the control arm (usually the previously approved regimen).

With respect to study duration, Merck Study 069, which compared indinavir 1200 mg bid to indinavir 800 mg tid both in combination with 2 NRTI, is a prime example supporting the use of longer studies to evaluate differences between dosing regimens. In this study, both regimens appeared to be performing similarly at 16 weeks. However, at 24 weeks there was a substantial difference in virologic response for the two regimens favoring the three times daily indinavir regimen.

The division currently recommends studies that are sufficiently powered to demonstrate either superiority or equivalence. For the latter a delta of 10-12% has been recommended for sample size calculations. For a two-arm study in treatment naïve individuals assessing the proportion of patients with HIV RNA levels below 400 copies/mL, this may require a sample size of hundreds of patients. Because we recognize that such a study is quite resource intensive, we are interested in considering how PK/PD evaluations might help to make this process more efficient in terms of patient resources.

Issues Pertaining to Drug Interactions and Pharmacologic Enhancement

Combination regimens containing more than one PI and/or NNRTI often require dose adjustments due to drug interactions. Also, the development and clinical use of several approved and investigational PIs are increasingly being linked to coadministration with ritonavir, both to decrease pill burden and to increase efficacy. In some cases low dose ritonavir is used solely as a pharmacologic enhancer, in other cases both the antiviral and pharmacologic enhancing effects of ritonavir are sought. The regulatory issues associated with drug interactions and pharmacologic enhancement may be complex. Several different scenarios could be envisioned.

A sponsor may want to include information in their label regarding how to dose their PI or NNRTI concomitantly with other PIs or NNRTIs, as they would for many other drugs. Based on a PK interaction study the sponsor may be able to choose doses of the PIs and/or NNRTIs that yield similar concentrations (C_{max}, AUC and C_{min}) or perhaps slightly higher concentrations than the approved doses. Labeling of the drug interaction

may be straightforward, depending on the available safety data. Depending on the complexity of the particular drug interaction, labeling decisions may be more difficult.

A sponsor may study their PI or NNRTI with low dose ritonavir (or another drug that may inhibit hepatic metabolism) primarily for its pharmacologic enhancing effect. In this case, the dose and dosing frequency of the PI or NNRTI might be quite different from the approved regimen. PK parameters would also change, possibly resulting in an increase in all PK parameters or perhaps an increase in only Cmin, with similar AUC and Cmax or even reduced Cmax. Based on PK there may be several reasonable doses for either the PI or NNRTI and ritonavir, none of which would provide comparable exposure to approved regimens. Perhaps the metabolic inhibition would result in increased levels of metabolites, some of which might have unrecognized toxicities at higher concentrations. In this case how much additional efficacy and safety data should be required to make dosing recommendations in a drug label? What PK parameters are most important in choosing among dosing possibilities? These are some of the issues that we would like the committee to address.

The following sections include the draft agenda and questions for July 25. We realize that the agenda is quite ambitious for a single day; however, we view this as an opportunity to begin to grapple with these issues in an open public forum. We look forward to the committee's input into the many difficult issues regarding alternate dosing regimens. We hope that you will find some of the attached articles helpful in preparation for this day.

Agenda and Advisory Committee Questions

July 25, 2000 Agenda

8:30 Welcome
8:35 Conflict of Interest Statements
8:45 Introduction/Opening Remarks – Heidi Jolson
9:00 Biopharmaceutics/Clinical Overview – FDA
10:00 Break
10:15 Anti-infective Perspective – Alex Rakowsky
10:45 Antiretroviral PK/PD Overview – Richard Hoetelmans
11:15 Future Considerations for PK/PD Research – Terry Blashcke
11:45 Lunch
1:00 Open Public Hearing
2:00 Committee Discussion / Regulatory Examples

Questions

PK/Efficacy Issues:

1. What is the role of pharmacokinetic data in the evaluation of new formulations and alternative dosing regimens for approved antiretroviral drugs? Given the available data, please discuss the strengths and limitations of specific pharmacokinetic parameters such as AUC and C_{min} in predicting virologic response.

A. What data are needed to rule out the contribution of any pharmacokinetic parameters to efficacy?
B. What is the role of intracellular concentrations in the evaluation of new formulations and alternative dosing regimens for approved NRTIs?
C. In what circumstances would clinical efficacy data be necessary?

PK/Safety Issues:

2. Do the scientific data at present correlate any particular pharmacokinetic parameter with toxicity?

    A. What amount and duration of safety data are needed to support new formulations/new dosing regimens of approved antiretroviral drugs with increased AUC/Cmax/Cmin?

Drug Interaction Issues

3. Which pharmacokinetic parameters should be considered when providing labeling information on concomitant administration of drugs? How should several dosing possibilities be addressed? In what circumstances are clinical data necessary?

Pediatric Issues:

4. Once an alternate regimen has been identified in adults, should we require identical PK profiles in children (i.e., all PK parameters equivalent) or only equivalent critical parameters (i.e., AUC or Cmin)? Does this apply to all drugs and all pediatric sub-populations or are there some situations in which more clinical/virologic data will be necessary?

Future Research Issues

5. What kinds of studies are needed to better define pharmacokinetic/pharmacodynamic relationships for approved antiretroviral drugs?