

## MEMORANDUM

TO: Members, Advisory Committee for Pharmaceutical Science

FROM: Ajaz S. Hussain, Ph.D.  
Deputy Director, Office of Pharmaceutical Science

Date: 10 April 2002

RE: 7 - 8 May 2002 Meetings of the Advisory Committee for Pharmaceutical Science

Dear ACPS Members,

We look forward to meeting you in May 2002 to discuss several important scientific topics. The first day of the meeting will primarily focus on two biopharmaceutics topics; regulatory recommendations on bioequivalence studies under fed conditions and approaches for expanding the regulatory applications of the Biopharmaceutics Classification System. Also, on the first day we will share with you our thoughts on discipline-specific subcommittees.

The second day of this meeting will focus on PAT Subcommittee (progress report and next steps), follow-up discussion on rapid microbial testing (should this topic be made part of the PAT subcommittee), PQRI recommendations on blend uniformity analysis, and a new "awareness" topic on polymorphism.

A brief summary of these topics and issues for discussion along with background information is attached. I hope this will help you in formulating your advice to us on these topics.

See you in May.

## **Summary of the discussion topics:**

### **Future Sub-committees**

Discipline specific sub-committees, under ACPS, are being considered as a means to expand the range of scientific expertise needed to address the wide range of scientific questions that arise within the Office of Pharmaceutical Science. We plan to discuss this concept with you.

- Proposal to form discipline specific subcommittees under ACPS
  - Clinical Pharmacology
  - Pharmacology/Toxicology (NCSS)
  - Microbiology
  - Manufacturing (PAT)
  - Others (?)

### **Draft Guidance: Food Effect BE Studies**

The draft guidance on food effect bioavailability and bioequivalence studies is the subject of this discussion. We plan to focus this discussion on the following questions on bioequivalence (BE) implications of the recommendation in this draft guidance.

1. With regard to waiver of *in vivo* fed bioequivalence (BE) studies in Abbreviated New Drug Applications (ANDAs) for BCS Class I drugs/drug products:

1.1 To what extent does the committee feel that the literature, in-house and original research data provide sufficient evidence to support the claim that fed BE studies are unnecessary?

[Note: We have recently completed our research studies (in collaboration with Univ. Tennessee) in which we assessed bioequivalence between generic drug products (model drugs studied: metoprolol (BCS-Class I; first pass metabolism), propranolol (BCS-Class I; first pass metabolism) and hydrochlorothiazide (BCS-Class III)) under fed conditions. These products were found to be bioequivalent.]

1.2. If additional evidence were needed to support the waiver of *in vivo* fed BE studies for BCS Class I drug/drug products, what form of evidence would be desirable?

2. With regard to using confidence intervals and a criterion to claim bioequivalence between fasted and fed states for new drugs and between fed states for generic drugs (relative to reference products):

2.1 To what extent does the committee feel that the issue of food effects can be treated as a lack of equivalence question?

2.2 To what extent does the committee feel that a 90% confidence interval with boundaries of 80-125% are appropriate to make a claim of bioequivalence?

2.3 What alternative approaches would the committee suggest to demonstrate bioequivalence in the fed state?

## **Biopharmaceutics Classification System - Next Steps**

### **Background: Scientific Basis for Current BCS Based Biowaivers**

The FDA/CDER's BCS guidance (9/2000) document provides a means for justifying biowaivers for rapidly dissolving products (85% in 30 minutes in 900 ml of 0.1 N HCl, 4.5 pH and 6.8 pH media, in USP I or II) of highly soluble (highest dose strength soluble in 250 ml in pH 1-7.5 range) and highly permeable (extent of absorption equal to, or greater than 90%) drugs that are not considered to exhibit a *Narrow Therapeutic Range*.

The high permeability plus high solubility attributes are utilized in this guidance to minimize risk of bio-in-equivalence due to solubility or permeability limited absorption processes. Low permeability drugs exhibit incomplete absorption from small intestine and, therefore, small intestinal residence time of these drugs (dissolved) is considered critical. Relatively minor differences in the time needed for complete *in vivo* dissolution of low permeability drugs can potentially reduce the time available for their absorption during small intestinal transit.

The rapid dissolution (in three different pH conditions) and built-in profile similarity criteria are to ensure that dissolution *in vivo* is not likely to be rate limiting and minimal differences in product disintegration time (to minimize the likelihood of differences in gastric emptying) are observed between the pre- and post change products. The multi-media dissolution is recommended to account for observed physiologic (and pathologic) variability in gastric fluid pH and gastric emptying process. Since the time of drug administration (during bioequivalence studies and use by patients) is not synchronized (and should not be for practical reasons) with the gastric motility pattern, gastric emptying in some subjects could occur almost immediately after administration. In such cases dissolution would occur in small intestine following emptying. If one of the two products being compared exhibits a different dissolution rate (compared to the other product) in intestinal pH then the effect of variable gastric emptying on *in vivo* dissolution may not be a truly random phenomenon. This may increase the likelihood of bio-in-equivalence when only a single *in vitro* dissolution condition (e.g., 0.1 N HCl) is used to compare two products.

The multi-media dissolution criteria are intended to minimize this possibility.

The permeability attribute of drugs plays a significant role in the request for biowaivers. In addition to reasons stated above, permeability contributes to the development of "sink condition" for *in vivo* drug dissolution. Drug dissolution *in vitro* in a relatively large volume, 900 ml, is likely to be a better emulation of *in vivo* dissolution process of a highly permeable drug. High permeability attribute also reduces the probability of excipient affecting bioavailability due to an effect on gastrointestinal membranes and/or motility.

### **Focus of Discussion:**

The current guidance has been criticized as being "too conservative" with respect to its application for biowaivers. FDA staff and invited guests will present to you some proposals on how to expand the applications of BCS.

Questions for the Committee:

- (1) Should the Agency consider expanding the application of BCS based biowivers to rapidly dissolving conventional (IR) products of Class III (high solubility and low permeability) drugs? If so, what evidence should the agency collect to justify this extension?
- (2) Should the Agency consider expanding the application of BCS based biowivers of conventional (IR) solid oral products of Class II (low solubility and high permeability) drugs that exhibit similar *in vitro* dissolution? If so, what evidence should the agency collect to justify this extension?

### **Process Analytical Technology**

Two presentations are planned:

1. PAT Subcommittee report (Tom Layloff)
2. Progress report and next steps (Ajaz Hussain)

### Accomplishments to Date

Following the November 2001 FDA Science Board and ACPS meetings the following has been accomplished:

1. Formation of CDER-ORA Steering Committee on PAT

Membership: Douglas Ellsworth (Director, New Jersey District Office, ORA), Mike Olson (Director, Field Science, ORA), Joe Famulare (Director, Division of Manufacturing and Product Quality, CDER), Frank Holcombe (Associate Director for Chemistry, Office of Generic Drugs, CDER), Moheb Nasr (Acting Director, Office of Testing and Research, CDER), Yuan-yuan Chiu (Director, Office of New Drug Chemistry, CDER), Ajaz Hussain (Chair).

Two parallel tracks identified for facilitating PAT.

The first track will develop general guidance on PAT to provide a regulatory process for PAT based submissions and to articulate regulatory expectations for both review and inspection. The information necessary for this guidance will be obtained from industry and academic experts on the FDA's PAT Subcommittee under the Advisory Committee for Pharmaceutical Sciences.

The second track will encourage companies to submit their PAT based applications. A CDER-ORA (Review-Inspection) team approach will be utilized to work with these companies to address questions as they arise, so as to minimize "regulatory uncertainty." We are very pleased to report that as of March 8, 2002, two US companies have officially requested meetings with FDA to discuss their planned PAT based submissions.

## 2. PAT- Subcommittee

In response to our Federal Register notice we received over 60 applications from industry and academia to serve on this subcommittee. The members were selected to represent the key scientific and engineering disciplines necessary for PAT. In addition, four working groups were created to have focused discussions on the following topics: (1) Benefits and Regulatory Hurdles, (2) Process and Analytical Validation, (3) Product Development, and (4) Chemometrics. The first meeting of this subcommittee was held on 25-26 February 2002. This was a very successful meeting and very useful information was collected.

## 3. Field Trips

Several companies invited FDA staff to visit their facilities and to discuss the PAT initiative. We visited Bristol-Myers Squibb Company in New Jersey, Pfizer in Friberg (Germany) and AstraZeneca in Plankstad (Germany). Both the German plants have PAT based manufacturing systems in place. The AstraZeneca plant is currently completing their validation studies (for German Authorities) on a complete PAT based system for production of tablets of two very potent drugs.

## Planned Next Steps

1. Establish a CDER-ORA PAT team for joint review/inspection of PAT based submissions. We are planning to identify four reviewers and four inspectors to be part of this first team. These individuals will then be trained on PAT systems.
2. Develop a training (and certification) program of the PAT Review-Inspection Team.
3. Expand FDA research efforts to understand issues related to PAT based applications.
4. Develop the proposed general guidance on PAT following the second meeting of the PAT-Subcommittee. Publish draft for comments and input.
5. Public workshops on PAT.

## **Rapid Microbial Testing - Update**

Is the PAT program sufficiently broad to address the general issues related to the introduction of rapid microbial testing?

## **Blend Uniformity**

At the previous meeting of the ACPS we introduced this topic to you. We have now received the official recommendation from the PQRI and wish to discuss these with you prior to adopting or incorporating these in our revised guidance document. The questions for the ACPS considerations are:

Do you consider the PQRI proposal appropriate for inclusion in a planned revised FDA guidance? If no, please suggest modifications or improvements.

If yes, should the proposed stratified sampling and analysis plan be applicable only for the bioequivalence batch and validation batches?

If the proposed stratified sampling and analysis plan is limited only to bioequivalence and validation batches, how should adequacy of mix be ensured for routine production batches?

Should the planned revised FDA guidance only focus on generic drugs or should it be a general guidance (i.e., for both new and generic drugs)?

(Note - our current thinking is that this is a science issue and not just limited to

generic drugs. Therefore, we believe the guidance should apply to both generic and new drugs).

### **Regulatory Issues related to crystal habits - polymorphism**

This topic will be presented to you as an "awareness" topic to seek your input to identify and frame the key questions. This topic plus the "awareness" topic on "physical" stability, discussed at the previous meeting, are in preparation for an in-depth discussion at a subsequent ACPS meeting.

FDA staff and invited experts will provide an overview on regulatory issues related to polymorphism. These presentations will cover regulatory issues related to characterization, setting specification for a new drug candidate (ICHQ6A guidance), and impact on approval of generic drugs.