

## Background Information for Advisory Committee for Pharmaceutical Science

October 20, 2004

# Bioequivalence Testing for Locally Acting Gastrointestinal Drugs

## Introduction

Bioequivalence (BE) is defined in 21 CFR 320.1 as “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.”

FDA usually considers that the plasma concentration of a drug is a surrogate for the concentration at the site of action for a systemically acting drug. 21 CFR 320.24 outlines options for bioequivalence testing:

- Pharmacokinetic (PK) studies
- Pharmacodynamic (PD) studies
- Well-controlled clinical trials
- In vitro tests
- Any other approach deemed adequate by FDA

For drugs whose site of action is the gastrointestinal (GI) tract, determination of bioequivalence is more complicated as local drug concentrations cannot be measured directly. The goal of this topic is to present to the committee background on some of the scientific issues involved in developing bioequivalence methods for locally acting drugs that target the GI tract. In the past FDA has acted on case by case basis, but for the future we would like identify the key scientific principles for consistent and efficient identification of bioequivalence methods. We would like ACPS input on the following issues related to bioequivalence of locally acting GI drugs

- Role of pharmacokinetic studies
- Role of in vitro tests including dissolution and binding assays
- Role of clinical studies

## Role of Pharmacokinetic Studies

While it is understood that pharmacokinetic (PK) studies of locally acting drugs are related to safety, it is very common to see statements that for locally acting drugs PK is not correlated with therapeutic effect. While this statement is often true, we need to carefully consider its implications for bioequivalence testing.

When a PK study is used to compare two products and evaluate bioequivalence, the quantities that are measured are the maximum plasma concentration  $C_{max}$  and the area under the plasma concentration versus time curve, AUC. However, since the two products being compared contain the same active ingredient, the differences between products can only result from differences in formulation performance much earlier in the absorption process (see Figure 1). By comparing PK results we make a conclusion as to whether there is a significant difference in formulation performance.

As the result of bioequivalence testing is to evaluate formulation performance as reflected in changes in  $C_{max}$  and AUC, it is clear that the connection of PK to product quality is the same whether the site of action is downstream or upstream. Figure 1 shows a schematic of a PK study on a systemic acting drug, while figure 2 shows a schematic of a PK study on a GI acting drug. In both figures, the connection between formulation performance and PK measurement is the same. For local acting drugs, blood concentration is disconnected from PD/clinical response but is still connected to product characteristics.

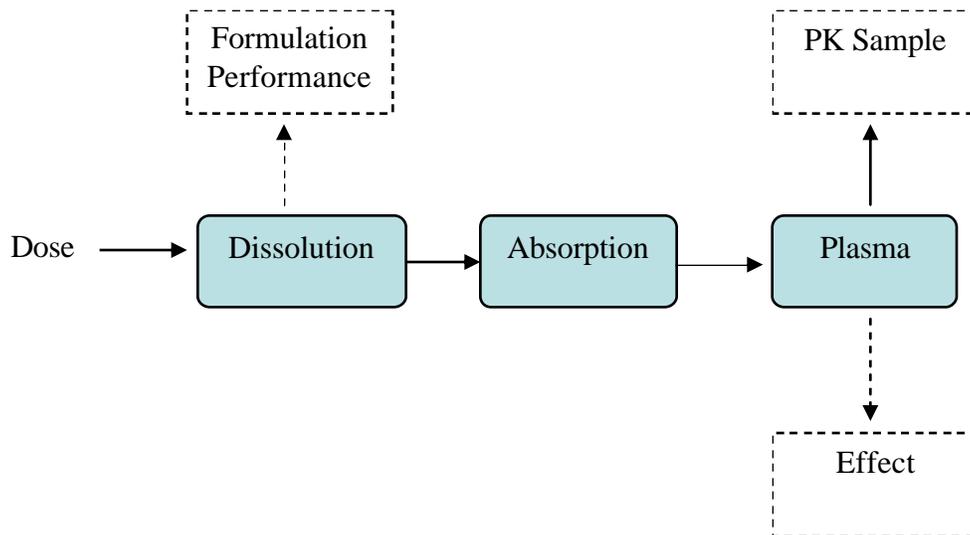


Figure 1: Systemic acting drugs

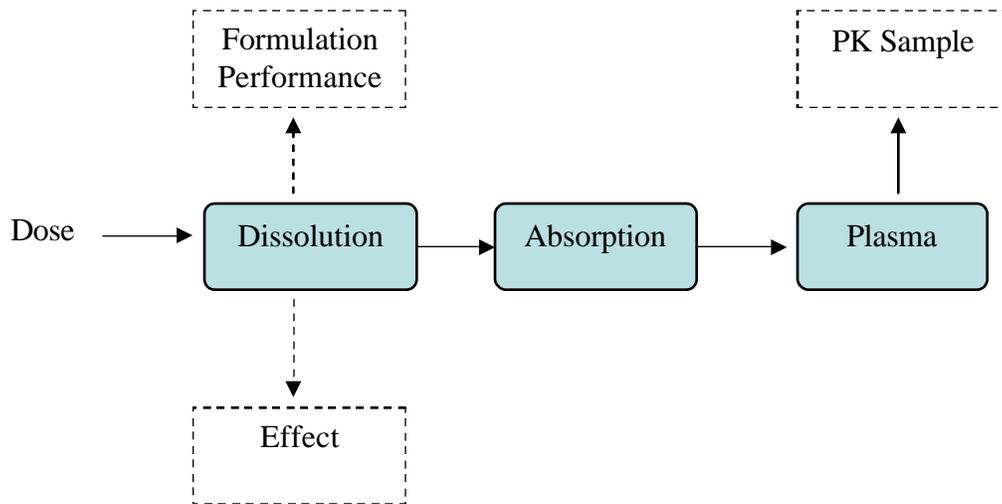


Figure 2: Locally acting GI drugs

However, when plasma levels can be connected to product effectiveness then we have an inherent way to determine what a significant difference in product performance is. When the connection to efficacy is broken, we do not have a simple way to say what difference in PK is significant. In this sense, downstream PK is similar to a PD endpoint for which a dose-response curve needs to be established.

Another concern about PK studies on locally acting drugs is that drug may be able to reach the plasma without passing the site of action. An example is an inhalation product for which some of the dose is swallowed and potentially absorbed orally. An important distinction is between parallel and sequential absorption paths. In the inhalation example, drug either goes to the lung or to the stomach or could appear in plasma at the same time by either path. In a locally acting GI drug the absorption process is sequential so drug absorbed from the intestine appears before drug absorbed in the colon and thus can be distinguished.

## Role of In Vitro Dissolution Testing and Binding Assays

Drugs that act locally in the gastrointestinal tract present difficult bioequivalence problems since often plasma levels are undetectable and measurements that are close to the site of action would be preferred. If we consider mesalamine as an example drug, it must reach the mucosal surface lining the gastrointestinal tract in order to exert its pharmacological effect. The determinant of the mesalamine concentration reaching the mucosal surface lining the gastrointestinal tract is the in vivo dissolution rate. In general, for locally acting GI drugs dissolution directly determines the rate and extent of delivery to the site of action (bioequivalence)<sup>1</sup>. This is different than for systemically

<sup>1</sup>One exception is rapidly dissolving GI acting drugs whose delivery to the intestine is limited by gastric emptying. These drugs could be covered under a BCS type waiver

acting drugs for which dissolution is only sometimes the controlling step. Thus for GI acting drugs we should focus more attention on dissolution testing for demonstrating bioequivalence. The main concern is, of course, how well in vitro dissolution reflects in vivo dissolution.

Some GI acting drugs are formulated to target different regions of the GI tract, often via coatings that lead to pH dependent dissolution. Comparative dissolution testing at different pH could demonstrate that test and reference products are targeting the same region of the GI tract. Figure 3 shows an example of comparative dissolution for mesalamine formulations in different media.

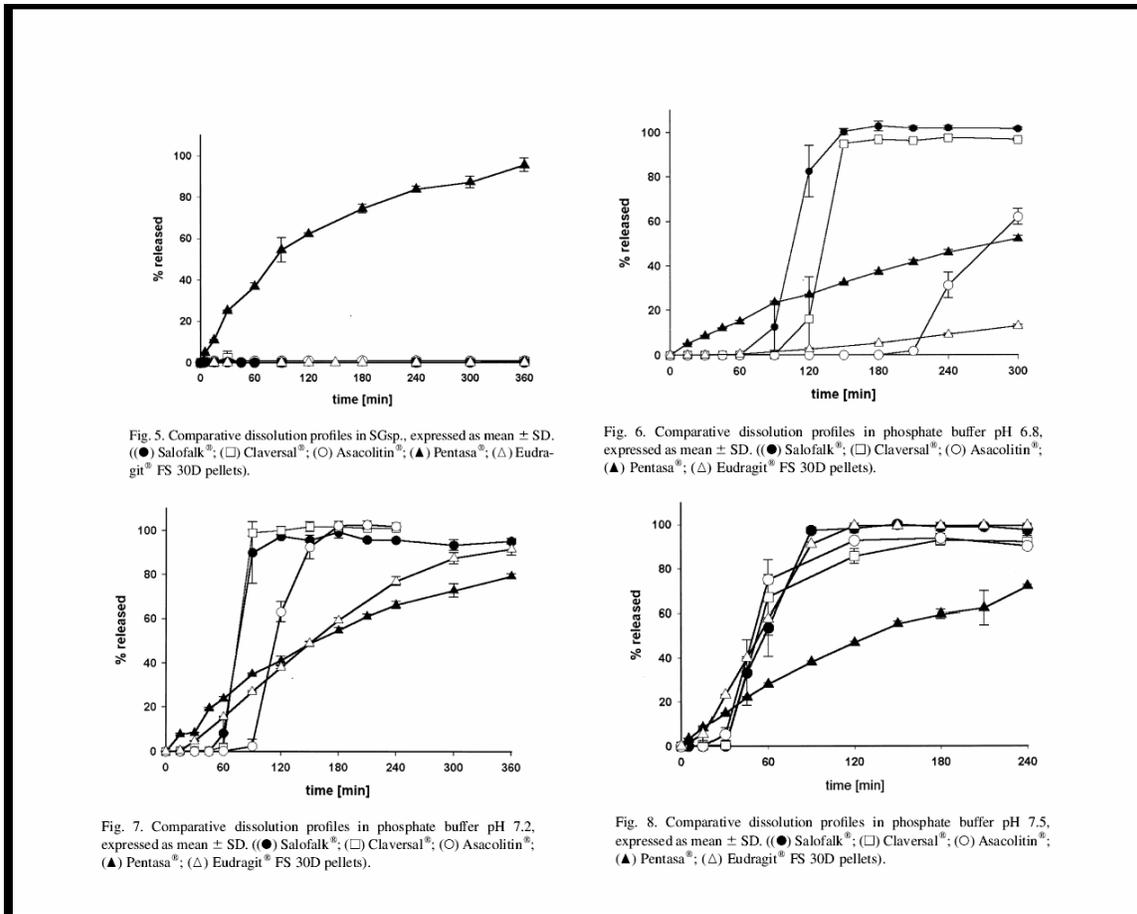


Figure 3: Comparative dissolution of mesalamine formulations in simulated gastric fluid and phosphate buffer pH 6.8, 7.2, and 7.8<sup>2</sup>

Biowaivers for BCS class I drugs formulated in rapidly dissolving immediate release solid oral dosage forms are well established<sup>3</sup>. Since a GI acting drug does not need to be absorbed,

<sup>2</sup> M. W. Rudolph, S. Klein, T. E. Beckert, H. Peterit, and J. B. Dressman. A new 5-aminosalicylic acid multi-unit dosage form for the therapy of ulcerative colitis. *Eur J Pharm Biopharm*, 51(3):183–190, May 2001.

application of the scientific basis of the BCS would suggest that a high solubility drug in a rapidly dissolving formulation with no excipients that affect product performance may be eligible for a biowaiver.

## **Clinical Studies**

Pharmacokinetic data from conventional bioequivalence studies are helpful in assessing the comparative safety profiles as well as being able to detect formulation differences. However, studies that measure the concentration of drug in the small intestinal mucosa could provide more direct evidence of equivalent tissue concentration at the site of action.

Currently, it is suggested that for some locally acting GI drugs, comparative clinical trials be conducted to demonstrate bioequivalence. Such studies need to show that the test product is equivalent to the reference product and also effective as compared to placebo. Comparative clinical studies are both very expensive and can often be insensitive to formulation differences. Therefore, clinical bioequivalence studies are used only when there is no other bioequivalence method available.

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<sup>3</sup> Waiver of In Vivo Bioavailability and Bioequivalence Studies for IR Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, 2002. *FDA Guidance for Industry*; Federal Drug and Food Administration: Rockville, MD, 2002.

## Topic Questions

We would like the committee to comment on the following questions:

- For locally acting GI drugs, is PK, if measurable, an *in vivo* test sensitive to formulation performance and useful as a part of a determination of bioequivalence?
- Are there any drug specific issues that would aid FDA in interpreting the results of a PK study on a GI acting drug with respect to a conclusion about bioequivalence?
- When is it possible to use dissolution testing alone to demonstrate bioequivalence of GI acting drugs?
- When should comparative clinical trial studies be conducted to demonstrate bioequivalence?