Revising Oral Pharmacokinetics, Bioavailability and Bioequivalence Based on the Finite Absorption Time Concept

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Dedicated to our children and grandchildren
Evangelos, Spiros, Andreas, Giorgos,
Artemis, Thalis, Stefanos, Panos and Amelia

Foreword

It is rare and refreshing to see a well-researched treatise that challenges a long-held scientific approach that obviously deserves scrutiny. Real-world oral pharmacokinetic curves not uncommonly show unexplained up-and-down patterns in the ascending or absorption part of overall bell-shaped concentration-time trajectories, followed by a sharp decline in concentration after the observed maximum concentration (C_{max}). Such datasets are not well modeled using conventional compartmental models. The long overlooked Finite Absorption Time (FAT) concept, as manifested in the Physiologically Based Finite Time Pharmacokinetic (PBFTPK) models described in this book, offers a sound theoretical foundation to address such shortcomings of conventional oral pharmacokinetic models. It may come as a delight to pharmaco metricians to be able to adequately fit oral pharmacokinetic curves with strange double peaks or zigzag patterns in the absorption portion of the curve, often attributed to randomness of data or experimental aberrations using conventional approaches.

As discussed in Chap. 7, the FAT/PBFTPK approach may contribute a supportive basis for regulatory recommendations to using partial AUC values (pAUC) for bioequivalence (BE) assessments. pAUC values can be usefully employed when a formulation change leads to a modified exposure response relationship without affecting C_{max} and AUC. For example, the FDA recommended the use of partial AUC pAUC determinations for demonstrating BE of generic zolpidem extended-release tablets and methylphenidate hydrochloride ER capsules in 2011. As of June 2022, the FDA has issued 44 product-specific guidances recommending the use of pAUC to determine BE for drugs submitted via an ANDA. Consideration for using pAUCs in BE metrics and the selection of time intervals to truncate the AUC are both drug- and formulation-specific. PBFTPK modeling can guide understanding of how a formulation interacts with segmental gastrointestinal physiology as reflected in the observed PK curves.

Critical evaluation is required of any new scientific approach that is proposed to improve on a long-practiced basis for characterizing PK and BE, which are key to evaluation of new or generic drugs. The authors are to be commended for challenging oral pharmacokinetic traditional models of drug absorption that perform poorly

in some circumstances. Via this well-written book, the scientific community can learn of the FAT concept and evaluate its value proposition seriously.

Disclaimer: This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

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Preface

According to the Editor of Journal of Pharmacokinetics and Pharmacodynamics Dr Peter Bonate [1] "in a few short years, quantitative systems pharmacology (QSP) has become a major tool available to pharmacometricians to improve decision making in drug development, so much so that today pharmacometrics can be broadly classified into three groups: population-based methods, physiologically-based pharmacokinetics (PBPK), and Quantitative Systems Pharmacology (QSP). Recently, we are starting to see the emergence of a fourth field: machine learning." This is so since science progresses. It evolves. New knowledge is created. Pharmacometrics is no exception [1].

In the midst of these dramatic changes, we realized in 2019 that a wrong assumption that breaks oral pharmacokinetics was used and extensively applied since 1953 [2]. In fact, the infinite time of oral drug absorption was conceived from the first day of the birth of pharmacokinetics when F. H. Dost introduced the term pharmacokinetics [2]. He adopted the function developed by H. Bateman [3] back in 1910 for the decay of the radioactive isotopes to describe oral drug absorption as a first-order process. We unveiled this false hypothesis relying on common wisdom, i.e., drugs are absorbed in finite time. This false assumption had dramatic effects on the evolution of oral pharmacokinetics, but most importantly on the bioavailability and bioequivalence concepts and metrics. Accordingly, the title of this book could be "*Unveiling the wrong assumption that breaks oral pharmacokinetics: Drugs are absorbed in finite time.*" Instead, we utilize a different title which places emphasis on the "*revision*" of the three major disciplines of biopharmaceutics-pharmacokinetics, namely, oral pharmacokinetics, bioavailability, and bioequivalence under the prism of Finite Absorption Time (FAT).

In oral pharmacokinetics, the absorption rate constant became the sole parameter for expressing quantitatively the rate of drug absorption in classical and population pharmacokinetic studies. However, it was found to be the most variable parameter with non-physiological meaning having units (time^{-1}), not allowing a valid interspecies or pediatric scaling and relying on the unphysical assumption of infinite time of absorption [4]. Twenty years ago or so when the development of PBPK models started, the assessment of the rate of drug input was based on permeability estimates,

namely, the PBPK models abandon the use of absorption rate constant for the assessment of the drug's input rate. Our work was based on the physiologically sound FAT concept [5]; thus, the relevant Physiologically Based Finite Time Pharmacokinetic (PBFTPK) models developed were found to be a powerful tool for the pharmacokinetic analysis of oral concentration, time data. The software developed is made available to the readers as supplementary electronic material (see http://sn.pub/PtsM9h).

In bioavailability studies, the area under the curve from zero to infinity $[\mathrm{AUC}]_0^\infty$, which corresponds to the indefinite integral of the concentration-time function describing the time course of drug in the body, wrongly became the golden metric for the extent of drug absorption. In reality, $[\mathrm{AUC}]_0^\infty$ is an ideal exposure metric; intuitively, the $[\mathrm{AUC}]_0^\tau$, where τ is the FAT, is the proper metric for the extent of drug absorption. In parallel, $C_{\max}$ is currently used as an absorption rate metric. Under the FAT concept, the concentration at time τ, $C(\tau)$ corresponds to drug concentration at the termination of the drug absorption process(es). In this vein, the numerical value of the observed maximum blood drug concentration equal to or greater than $C(\tau)$ should be used as such. This means that the magnitude of its difference between reference and test formulations in bioequivalence studies should be specified on pharmacological-pharmacodynamic basis for each one of the drugs examined. For example, critical dose drugs with narrow therapeutic index, e.g., cyclosporine, can have a smaller absolute difference and/or an upper/lower boundary for the test and reference formulations. These considerations point to the abolishment of the term "rate" in the definition of bioavailability and the use of the relevant parameter $C_{\max}$ accompanied with statistical criteria as an indicator of the rate of absorption.

The book is divided into two parts. In Part I, the first two chapters are devoted to the mathematics associated with the unphysical hypothesis of infinite absorption time as well as the extensive use of the absorption rate constant in biopharmaceutics and pharmacokinetics since 1953. Chapter 3 focuses on the development of the FAT concept, while the relevant PBFTPK models are described in Chap. 4. In Part II, Chap. 5 relies on the historical aspects of the bioavailability and bioequivalence concepts. The evolution of bioequivalence studies for the establishment of therapeutic equivalence of test and reference formulations is the subject of Chap. 6. Bioavailability is analyzed under the prism of the FAT concept in Chap. 7. Methodologies for the estimation of absolute bioavailability from oral data exclusively are reported for the first time. In Chap. 8, a methodology towards the revision of the bioequivalence assessment is presented.

This book is intended for academics/students or scientists working in pharmaceutical industries, regulatory agencies, and contract research organizations. It can be used for teaching purposes in undergraduate courses dealing with biopharmaceutics, pharmacokinetics, and biomedical engineering. However, the content of Chap. 4 and the relevant PBFTPK software applications are suitable for postgraduate courses of these disciplines. In parallel, as already mentioned, the use

of the PBFTPK software is made possible to the readers through the electronic supplementary material accompanying this book.

A number of obvious applications of the FAT concept for pharmacometricians to important topics have not been included in this edition. For example, all software dealing with oral drug absorption in PBPK modeling work generates percent absorbed versus time profiles which are distorted and shifted to the right. This is the net result of the integral from zero to infinity applied to solve the differential equations describing the rate of the drug input processes. In a similar vein, in vitro in vivo correlations require reconsideration since all methodologies applied, c.f., Wagner-Nelson, Loo-Riegelman, and deconvolution techniques for the %absorbed versus time curve, utilize $[AUC]_0^{\infty}$ and not $[AUC]_0^{\tau}$ in the numerical integration step. In oral, pulmonary and intranasal pharmacokinetic and pharmacokinetic–pharmacodynamic population studies, the structural models used so far do not include the duration of absorption, τ as a fundamental parameter of the model. This is particularly so for studies under fed conditions; the PBFTPK models developed herein are the most suitable to be used in population Pharmacokinetic–Pharmacodynamic studies. Similar applications to interspecies and pediatric scaling can be also envisaged.

The book was conceived the summer of 2021 when we realized that the estimation of absolute bioavailability can be achieved from oral data exclusively.

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NOTE: The Electronic Supplementary Material of this book can be accessed at http://sn.pub/PtsM9h or via this QR.

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