

Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Workshop summary report

Challenges and opportunities in establishing scientific and regulatory standards for assuring therapeutic equivalence of modified-release products: Workshop summary report

Mei-Ling Chen^{a,*}, Vinod P. Shah^b, Derek Ganes^c, Kamal K. Midha^d, James Caro^e, Prabu Nambiar^f, Mario L. Rocci Jr.^g, Avinash G. Thombre^h, Bertil Abrahamssonⁱ, Dale Conner^a, Barbara Davit^a, Paul Fackler^j, Colm Farrell^g, Suneel Gupta^k, Russell Katz^a, Mehul Mehta^a, Sheldon H. Preskorn^l, Gerard Sanderink^e, Salomon Stavchansky^m, Robert Temple^a, Yaning Wang^a, Helen Winkle^a, Lawrence Yu^a

^a U.S. Food and Drug Administration, United States^b International Pharmaceutical Federation (FIP), The Netherlands^c Taro Pharmaceuticals, United States^d University of Saskatchewan, Canada, and FIP, The Netherlands^e Sanofi Aventis, United States^f Vertex Pharmaceuticals, Inc., United States^g ICON Development Solutions, United States^h Pfizer, Inc., United Statesⁱ AstraZeneca, Sweden^j Teva Pharmaceutical Industries, Ltd., United States^k Impax Labs, United States^l Clinical Research Institute and University of Kansas, United States^m University of Texas at Austin, United States

ARTICLE INFO

Article history:

Received 11 March 2010

Accepted 21 March 2010

Available online 27 March 2010

Keywords:

Bioequivalence

Therapeutic equivalence

Pharmaceutical equivalence

Interchangeability

Modified release

Partial area-under-the-curve

ABSTRACT

Modified-release products are complex dosage forms designed to release drug in a controlled manner to achieve desired efficacy and safety. Inappropriate control of drug release from such products may result in reduced efficacy or increased toxicity. This workshop provided an opportunity for pharmaceutical scientists from academia, industry and regulatory agencies to discuss current regulatory expectations and industry practices for demonstrating pharmaceutical equivalence and bioequivalence of MR products, further facilitating the establishment of regulatory standards for ensuring therapeutic equivalence of these products.

Published by Elsevier B.V.

1. Introduction

This report provides a summary of the workshop entitled “Challenges and Opportunities in Establishing Scientific and Regulatory Standards for Assuring Therapeutic Equivalence of Modified

* Corresponding author at: Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, Building 51, Rm. 4108, Silver Spring, MD 20993-0002, United States.
Tel.: +1 301 796 1658; fax: +1 301 796 9997.

E-mail address: Meiling.Chen@fda.hhs.gov (M.-L. Chen).

Release Products” held on October 1–2, 2009, Baltimore, MD, USA. The workshop was co-sponsored by the American Association of Pharmaceutical Scientists (AAPS), the International Pharmaceutical Federation (FIP), and the Product Quality Research Institute (PQRI).

Modified-release (MR) drug products are complex dosage forms designed to release drug in a controlled manner to achieve desired efficacy and safety profiles. Continued advances in pharmaceutical sciences have given rise to modern technological processes for controlled release formulations. These have produced drug delivery systems such as novel MR dosage forms to achieve optimal target product profiles. Inappropriate control of drug release from

such products may result in reduced efficacy or increased toxicity. Given the unique features and complexities of these products, challenges have been faced by industry and regulatory scientists in ensuring pharmaceutical equivalence, bioequivalence and therapeutic equivalence. The goals and objectives of this workshop were to:

1. Review advances in pharmaceutical science and technology for oral MR dosage forms and assess their potential impact on the establishment of scientific and regulatory approaches to evaluating therapeutic equivalence of these products.
2. Review current regulations/regulatory guidance and industry practices for demonstrating pharmaceutical equivalence, bioequivalence and therapeutic equivalence of oral MR products.
3. Examine current and emerging issues regarding equivalence determination of these MR formulations, and provide systematic analyses for problem solving.
4. Elucidate critical factors governing oral MR product performance *in vivo* and consider innovative approaches for demonstrating or supporting therapeutic equivalence of these products and
5. Identify the critical paths to establishing scientific and regulatory standards for ensuring therapeutic equivalence of oral MR products.

The two-day workshop provided an opportunity for pharmaceutical scientists from academia, industry (innovator and generic companies) and regulatory agencies to have open discussions on current regulatory expectations and industry practices for demonstrating pharmaceutical equivalence and bioequivalence of oral MR products, facilitating the establishment of scientific and regulatory standards to ensure therapeutic equivalence of orally administered MR dosage forms. This summary report highlights the presentations, key ideas and recommendations discussed at the workshop.

2. Characteristics of modified-release dosage forms

MR dosage forms are those dosage forms whose drug-release properties are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release (IR) dosage form. According to the U.S. Food and Drug Administration (FDA) and U.S. Pharmacopeia (USP), MR solid oral dosage forms comprise delayed and extended release drug products. In addition to the delayed and/or prolonged release characteristics, newer oral MR products may also exhibit pulsatile-release, chrono-release or targeted delivery (e.g., colonic delivery), etc. Moreover, some of the oral MR products in the marketplace include combinations of IR, delayed release, and/or extended release components. These dosage forms may be designed to deliver drugs in a controlled and predictable manner over a period of time or at a predetermined position in the gastrointestinal (GI) tract.

Several commercial oral MR products have been developed using platform technologies such as hydrophilic matrix tablets, osmotic systems, and multi-particulate tablets. To better predict the *in vivo* performance of MR products, it is pertinent to understand how the product was designed, the attributes of the technology employed, and the mechanism and kinetics of drug release from the dosage form. Equally important is the understanding of biopharmaceutical properties of the dosage form, such as GI transit and regional absorption of the drug in the GI tract. Biopharmaceutics is focused on the mechanisms behind the absorption of an active drug molecule and its transport to the target site in the body. The key aspects of this process for an orally administered MR formulation intended for systemic absorp-

tion may include transit time of the formulation in the GI tract, location of drug released from the formulation, dissolution of the active molecule, permeation through the GI membrane, first pass clearance/pre-systemic metabolism, and intestinal degradation (especially bacteria-mediated reductive degradation in the colon). GI transit course is of special relevance for MR products since formulation design could potentially alter the transit properties, thereby influencing drug absorption. Drug-release course and dissolution profile are the fundamental properties for an MR formulation, which needs to be well understood in order to predict the performance of the product. Intestinal permeability and GI metabolism also deserve special attention for MR formulations in view of regional variations in the GI tract.

In vitro dissolution is one of the most important tests in the development of an MR dosage form and it is essential to develop and implement *in vitro* dissolution tests that are capable of predicting *in vivo* performance whenever possible. However, this can be challenging in the presence of varying physiological conditions (e.g., pH, shear forces, and enzymes) along the GI tract, including food effects and/or ethanol intake. It is further noted that a dissolution method that discriminates between formulations does not always translate into a method that predicts performance *in vivo*. The development of a predictive dissolution method is commonly dependent upon a number of factors, the most important of which is the matrix and/or technology used to modify the rate of drug release. Consequently, for generic drug development where MR mechanisms are often not the same as the branded product, it is rare that one dissolution method might be useful or predictive for both products.

3. Regulatory approval of modified-release products in new drug applications

In principle, FDA approval of MR products in new drug applications (NDAs) submitted by innovator firms is based on evidence of an adequate drug exposure–response framework. Exposure can be expressed by blood levels or dose, and response by validated clinical endpoint(s) or surrogate endpoint(s). The exposure–response framework should include knowledge of the impact that drug input rate and its delivery course have on response or established therapeutic range for the MR product under consideration. Preferably, a quantitative and predictive exposure–response relationship exists and tolerance does not develop over time.

In general, there are three types of NDAs for MR drug products: (a) IR to MR switch, (b) MR to MR switch with unequal dosing intervals, and (c) MR to MR switch with equal dosing intervals. Regulatory requirements vary with the type of NDA submitted to FDA. For example, in the case of switching from an IR to an MR product, the key question is whether there is an adequate exposure–response framework established by the previously approved IR product. If the answer is yes, no clinical efficacy trial may be needed and the only requirement is to conduct three clinical pharmacology studies under single-dose (fasting and fed) and steady-state conditions (U.S. Food and Drug Administration, 2009a). The main goal is to ensure that the new MR product has similar exposure course of the drug compared to the previously approved product with proven efficacy. If the answer is no, one efficacy and/or safety trial may be necessary in addition to the three clinical pharmacology studies.

In the clinical efficacy trial for the MR product, a head-to-head comparison between the MR and IR products is not considered a requirement, and thus NDA sponsors opt to do placebo-controlled studies without an IR formulation in the trial. This may be unsatisfying in view of the experiences from non-clinical studies. There have been several cases in which toxicity seen in animals dif-

fers depending upon the dosing regimen and toxicity is usually worse following a multiple-dose/day regimen relative to a single daily dose. Accordingly, NDA sponsors may be asked to perform animal studies with the appropriate regimen in addition to the clinical efficacy trial in patients. However, currently sponsors are not required to obtain much long-term safety data in humans or completely re-do non-clinical studies for an MR product. For antiepileptic drugs, the exposure–response relationship is usually in reference to trough levels that have been shown to reflect some drug effects. While equivalent areas under the curve (AUCs) assure similar effectiveness between IR and MR products, the question remains as to whether the shape of the curve matters in achieving the desired response. FDA always offers NDA sponsors the opportunity to provide adequate evidence that the shape of the plasma concentration–time curve has no effect on the effectiveness of the product under investigation. However, such data or information is difficult to obtain and thus is seldom provided by drug sponsors.

4. Establishing therapeutic equivalence of modified-release products

Drug products are considered to be *therapeutic equivalents* only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling and manufactured in compliance with current good manufacturing practice (cGMP) regulations (U.S. Department of Health and Human Services, 2010). In this setting, FDA deems drug products therapeutically equivalents when they meet the regulatory criteria of pharmaceutical equivalence and bioequivalence. Designation of therapeutic equivalence dictates interchangeability between a generic drug and its corresponding reference-listed drug (innovator) product. The following outlines the current standards, emerging issues and possible resolutions for documenting pharmaceutical equivalence and bioequivalence.

4.1. Pharmaceutical equivalence

In the U.S., pharmaceutical equivalents are referred to drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, and meet the identical or compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates (U.S. Food and Drug Administration, 2009b). Pharmaceutically equivalent drug products need not contain the same inactive ingredients and they may differ in their characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration dates/time, minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage conditions (U.S. Department of Health and Human Services, 2010). For simple dosage forms such as IR drug products, pharmaceutical equivalence may provide a presumption of therapeutic equivalence, which can be further verified by appropriate *in vivo* bioequivalence studies. In fact, these *in vivo* studies may be waived under certain circumstances, e.g., BCS Class I drugs formulated in rapidly dissolving products (U.S. Department of Health and Human Services, 2000). In the case of MR products, however, traditional appraisal of pharmaceutical equivalence may not provide a presumption of therapeutic equivalence. This is partly because *in vitro* and *in vivo* correlations (or relationships) might not have been carried out in the development of many MR products. In addition, excipients used for control of drug release are critical to the performance of MR products. To ensure therapeutic

equivalence of MR products, a scrutiny of pharmaceutical equivalence is essential, which may include careful characterization of physicochemical properties of the dosage form, purity of the drug substance and excipients, solubility, dissolution and stability of the drug/product. Further, it is of paramount importance to apply the quality-by-design (QbD) approach for development of a generic MR product. Under the QbD paradigm, the critical material attributes of release-controlling excipients should be identified. Excipients may be different between a generic and innovator MR product, but one has to make sure that such a difference is inconsequential. Similarly, release mechanisms may vary, but the generic product should have an equivalent rate, time course and extent of absorption to the reference product.

Application of the QbD approach requires determination of a quality target product profile (QTPP) as it relates to quality, safety and efficacy (U.S. Department of Health and Human Services, 2009). To define appropriate QTPPs for generic drugs, one should consider the clinical performance (e.g., pharmacokinetic profile and pharmacodynamic effect) as well as conditions of product administration (e.g., sprinkling capsule contents, splitting tablets, and GI physiology of the patient population). This is especially important in view of the fact that a lack of defining these target properties of relevance to ascertain clinical safety and efficacy may lead to non-equivalence between two MR products. Potential subject-by-formulation interactions can occur as a result of different performances between MR products in the presence of varying GI conditions that may be derived from GI physiology, food/fluid intake and formulation factors. It is noteworthy that several factors could influence the GI conditions of the patient population and in turn, alter the performance of an MR product. These factors may include pH/buffer capacity, drug solubility, excipient functionality, fluid flow in/out of an MR formulation, osmolarity/ionic strength, hydrodynamics/pressure forces, disintegration/erosion of formulation, food or ethanol intake, and difference in GI transit between formulations.

The QbD approach promises to build quality into a final product by prospectively designing formulations and processes to meet the predefined QTPP. To design a quality product, this approach calls for identification and controls of critical raw material attributes, process parameters, and sources of variability. In the meantime, raw materials and manufacturing process should be controlled to produce consistent quality over time. Tools are available for facilitating implementation of the QbD paradigm, which may include design of experiments (DoE), risk assessment and process analytical technology (PAT).

4.2. Bioequivalence

In the U.S. regulation, bioequivalence means “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” (U.S. Food and Drug Administration, 2009b). The current regulations recommend that drug sponsors conduct bioequivalence testing using the most accurate, sensitive, and reproducible approach available for the drug product under examination (U.S. Food and Drug Administration, 2009c). As such, pharmacokinetic studies with drug concentration measurement in blood/plasma have mostly been used for bioequivalence demonstration whereas pharmacodynamic studies or clinical equivalence studies are employed only when appropriate pharmacokinetic studies are not possible, e.g., bioanalytical methods are unavailable for measurement of a drug or its metabolite(s) in accessible biological fluids or blood/plasma concentrations do

not reflect drug availability at the site of action. The use of pharmacokinetic studies for bioequivalence evaluation suggests that equivalence in rate and extent of systemic exposure equates to similarity in clinical effectiveness and safety. While this holds for most orally administered drugs, there may be exceptions to the premise of predictive relationship between blood levels of drugs (and/or metabolites) and clinical efficacy/safety endpoints, for example, presence of time-dependent clinical response, genetic polymorphism in receptor expression at the site of action, or simultaneous occurring of multiple pharmacological responses.

Most pharmacokinetic studies for bioequivalence demonstration are conducted with single-dose, two-treatment, two-period, crossover design in a limited number of healthy volunteers (e.g., 24 subjects). Patient populations are recommended for bioequivalence studies in cases where there is safety concern for the drug under investigation. For orally administered MR products, two single-dose studies are necessary for documentation of bioequivalence – one under fasting and the other under fed conditions (U.S. Department of Health and Human Services, 2003). Currently, FDA does not require multiple-dose studies for bioequivalence demonstration between innovator and generic MR products. It remains a question as to whether such studies are necessary for some complex MR dosage forms. Bioequivalence studies are generally conducted on the highest strength, but a lower strength may be used if there is safety concern for administering high dose to healthy subjects (U.S. Department of Health and Human Services, 2003). Pharmacokinetic measures, including area-under-the-curve to the last measurable concentration (AUC_{0-t}), area-under-the-curve to time infinity ($AUC_{0-\infty}$) and maximum concentration (C_{max}), are obtained from the plasma concentration versus time profiles and subjected to statistical analysis. The current bioequivalence limit for these metrics is 80–125% based on a confidence interval approach (U.S. Department of Health and Human Services, 2003). Statistical comparison is not performed for the time to maximum concentration (T_{max}) since it is a discrete measure and highly dependent on the frequency of blood sampling. To guard against any potential clinical consequences, however, FDA routinely evaluates notable differences in T_{max} between products.

In the context of bioequivalence testing based only on AUC and C_{max} comparisons, the ability to substitute one product for another with no concern for differences in efficacy and/or safety (i.e., interchangeability) may depend on the following two factors: (a) the sensitivity of some or all of the drug effects to acute differences in concentration and (b) the close similarity of pharmacokinetic profiles of drug products in comparison. To determine if T_{max} and/or the shape of a plasma concentration–time curve are important for assessment of interchangeability, one should address the question of what possible effect might arise as a result of such a difference in concentration. Among other factors, the sensitivity to such concentration differences may rely on (i) rapidity of onset and offset of effect (for both therapeutic and possible adverse effects), and (ii) where the doses used clinically are located on the dose–response (or concentration–response) curve.

4.2.1. Rapidity of onset and offset of effects

It is noted that FDA considers two products to be bioequivalent in the presence of different rates of absorption if such differences in rate (a) are intentional and are reflected in the labeling, (b) are not essential to the attainment of effective body drug concentrations on chronic use, and/or (c) are considered medically insignificant for the particular drug product studied (U.S. Food and Drug Administration, 2009d). Theoretically, the above scenarios may apply to a number of drugs that take days or weeks to achieve their steady-state concentrations and exert their optimal effects, which then persists for days to weeks when the drug is

stopped. These drugs may include beta-blockers (effect on blood pressure), angiotensin-converting enzyme (ACE) inhibitors, antidepressants (e.g., bupropion, see Appendix A), antipsychotics, platelet inhibitors, lipid-lowering drugs, and most tumor-necrosis-factor (TNF) blockers. Drugs with slow onset of action seem to have little possibility of conferring differential effectiveness based on differences in T_{max} or shape of the plasma concentration–time profile. Dosing patterns may not be important for slow onset drugs, but these can be critical for drugs with a rapid onset of effect such as sleep aids (e.g., zolpidem, see Appendix A) and drugs for the treatment of attention deficit hyperactivity disorder (ADHD, e.g., methylphenidate, see Appendix A). Similarly, high dose of alpha blocker from a rapidly releasing formulation or dose-dumping from a controlled release product could/would be of a concern because of the consequential effects on blood pressure.

4.2.2. Where on the dose–response (or concentration–response) curve?

To evaluate the sensitivity of an acute difference in concentration(s), another factor that should be considered is where the clinical doses/concentrations fall on the dose–response (or concentration–response) curve. It has been observed that innovator firms tend to choose clinical doses/concentrations on or near the plateau of a dose–response (or concentration–response) curve for drugs with little dose-related toxicity. In such circumstances, small changes in dose or release rate will not significantly alter clinical response regardless of whether the drug effect is prompt or delayed. In contrast, for drugs with multiple therapeutic indices, small changes in dose may have a profound effect on adverse events and/or therapeutic effects. Some drugs such as *narrow therapeutic range/ratio* (NTR) drugs are only dosed on the steep part of their dose–response (or concentration–response) curves and thus it is likely that a modest difference in dose or release rate will make a significant change in their clinical outcomes. There are only few NTR drugs on the market because they are difficult to use clinically. These agents may include many oncologic drugs, some antiepileptics, and those drugs that need careful titrations in the clinical setting. In practice, small differences in the rate of drug release or absorption would not lead to different clinical outcomes for drugs exhibiting both delayed therapeutic effects and delayed adverse reactions. On the other hand, delayed therapeutic effect but rapid adverse reaction could be a situation where rate differences between products would cause concern for interchangeability.

Overall, if a drug has rapid therapeutic effect(s) and is dosed on the steep part of the dose–response curve, differences in the rate of drug release and shape of the pharmacokinetic curve could result in clinical differences. For such drugs, one would need to pay close attention to T_{max} , and broadly to the shapes of their pharmacokinetic curves.

5. Need for additional measures to assess bioequivalence

It is generally agreed that the present regulatory criteria are adequate in the assessment of bioequivalence for many MR formulations with conventional drug-release profiles in vivo. However, for MR products designed to achieve a rapid rise in drug plasma concentrations (and thus a rapid onset of therapeutic effect) following administration or newer MR products with different drug-release mechanisms (such as pulsatile- or chrono-release), other measures in addition to the current pharmacokinetic parameters (i.e., AUC and C_{max}) may be needed for assuring bioequivalence. In this context, several measures were suggested at the workshop, including the use of partial AUC at different times after dosing, application of similarity factor for comparison of shape of concentration–time

profiles, consideration of subject-by-formulation interaction using replicated or enrichment study designs, examination of within-subject variation and lot-to-lot variability, as well as conduct of clinical equivalence studies using biomarkers or surrogate endpoints.

The use of pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulations allows for linking drug concentrations to their effects (safety or efficacy), and thus can be used to assess the impact of a difference in input rate on therapeutic equivalence. While PK/PD modeling and simulations provide an additional perspective on therapeutic equivalence, PK/PD data may not furnish more information regarding therapeutic equivalence in comparison with PK data alone, because PK measures are more sensitive to detect the difference in input rate between formulations.

To consider any additional metric for bioequivalence of MR products, one should examine closely the time course of the response and nature of the exposure–response relationship. In addition, a series of questions ought to be addressed. For example, are there time-related effects, such as induction or tolerance, on drug action? Are plasma concentrations related to onset of response and/or duration of response? Is the response a function of steady-state concentrations? In the event that an additional metric is necessary, what is the appropriate metric? The metric of partial AUCs is currently proposed by FDA for a multiphasic MR product (zolpidem tartrate extended release) formulated to achieve rapid onset of action followed by sustained response. Determination of cutoff points for partial AUCs may have to be made based on the PK/PD or PK/response characteristics inherent in the drug and formulation under study. Additionally, within-subject variability associated with each partial AUC parameter chosen should be evaluated carefully. If the within-subject variability is high for a partial AUC, the reference-scaling approach employed for highly variable drugs may be applicable to the new measure. An ideal metric may not dramatically increase the sample size required for demonstrating bioequivalence as long as the PK profiles are similar between products in comparison. Population PK models may serve as a powerful tool in simulating various scenarios to evaluate the performance of new metrics and provide an insight into the relative impact of different formulations on bioequivalence outcomes.

6. Summary

The FDA's recent initiative on the application of quality-by-design (QbD) approach is important for developing and manufacturing MR products given the complexity of this dosage form. Under QbD, the relationship between formulation/manufacturing variables and quality target product profile is well understood, and thus these variables can be controlled to achieve the goal of pharmaceutical equivalence. The current regulatory approaches and criteria for evaluation of bioequivalence are considered adequate to ensure therapeutic equivalence and interchangeability of drug products in conventional monophasic (or monolithic) MR products. Nevertheless, additional measures may be necessary, from time to time, to establish bioequivalence of multiphasic MR products. Development of such measures should remain an important future objective. At this workshop, the metric of partial area under plasma concentration–time curve (partial AUC) proposed by FDA did receive a broad support as an additional measure for ensuring bioequivalence of multiphasic MR products designed for a rapid onset of drug action followed by sustained release. The cutoff for partial AUCs may be determined on the basis of the PK/PD or PK/response characteristics of drug products under examination, and the bioequivalence limits may be set based on the knowledge of within-subject variability from the reference product if the new metric is highly variable.

Appendix A. Case studies

A.1. Bupropion hydrochloride extended release products

Bupropion is a commonly prescribed antidepressant although the neurochemical mechanism of its antidepressive effect is unknown. Bupropion is a relatively weak inhibitor of neuronal reuptake of norepinephrine, serotonin and dopamine, and does not inhibit monoamine oxidase. Clearance of the drug has been found to be influenced by genetic polymorphism of CYP2B6.

The marketing approval of innovator bupropion HCl products (Wellbutrin) was first obtained for immediate release (IR) tablets, 100 mg, three times once-a-day dosing, followed by sustained release (SR) tablets, 150 mg, twice-a-day dosing, and subsequently extended release (XL) tablets, 300 mg, once-a-day dosing. While the SR formulation was approved based on pharmacokinetic equivalence to the IR formulation, the XL formulation was approved based on pharmacokinetic equivalence to the IR and SR formulation. Regulatory approval of the original IR formulation was on the basis of ascending dose trials with doses up to 900 mg/day. However, after approval but before marketing, a dose-dependent seizure risk was identified with bupropion. A re-analysis of the clinical trial data was judged to support its antidepressant efficacy at doses of 450 mg/day or less and thus marketing proceeded with a label modification to not exceed 450 mg/day. A clinical trial program was undertaken with the SR formulation but failed to provide convincing evidence of efficacy at dose of 400 mg/day or less. However, retrospective pooled analyses of four clinical trials revealed that remission rates for Wellbutrin SR, selective serotonin reuptake inhibitors (SSRIs, including fluoxetine and sertraline), and placebo were 45% ($N=507$), 45% ($N=504$) and 36% ($N=512$), respectively. The remission rates for Wellbutrin SR, fluoxetine, and sertraline were statistically superior to placebo in the pooled analysis, but not in two of the individual trials (data on file, GlaxoSmithKline). There are no independent trials demonstrating the efficacy of Wellbutrin XL tablets.

Bupropion exhibits a dose-dependent risk of seizure when doses exceed 450 mg/day (Davidson, 1989). There is evidence suggesting that seizure risk on bupropion may also be related to peak concentration of bupropion and/or one or more of its active metabolites (Davidson, 1989; Preskorn, 1991). Peak plasma levels of hydroxybupropion, a major metabolite, occur 7 h after administration of bupropion and are about seven times the peak level of the parent drug at steady state. The elimination half-life of hydroxyl metabolite is approximately 20 h, and its AUC at steady state is approximately 13 times that of bupropion. The other two minor metabolites have similar T_{max} values with hydroxybupropion. The relative contribution of bupropion and its metabolites to the efficacy or seizure risk is unknown. It is also unclear whether the efficacy of bupropion is dependent on the peak or steady-state concentrations of bupropion and/or its metabolites.

The efficacy of bupropion is often observed after dosing for 1–2 weeks. For extended release bupropion, maintenance of steady-state concentrations was the targeted therapeutic endpoint, which is due partly to the rapid and nearly complete metabolism of bupropion to three active metabolites. Modeling and simulation results indicated that subtle differences in the absorption rate of bupropion would yield negligible effects on the steady-state concentrations of its metabolites. Recently, there have been reports that some patients experience worsening of their depression following a switch from the branded to a generic extended release product. This may be due to the natural course of major depressive disorder (MDD) under treatment rather than a consequence of small pharmacokinetic differences between the two products that have met the regulatory bioequivalence criteria.

A.2. Methylphenidate hydrochloride extended release products

Methylphenidate is commonly prescribed medication for treatment of ADHD in children. Both IR and SR formulations of methylphenidate are currently available on the market. The IR formulation has short half-life and short duration of therapeutic effect (3–4 h), thereby requiring in-school and after-school dosing for most children. This formulation has a rapid onset of effect, but also yields fluctuations in peak and trough plasma levels upon multiple daily dosing. The SR formulation has a waxy matrix and behaves more like a slow release than a sustained release product. Zero-order release of methylphenidate in plasma leads to the development of acute tolerance to the drug (Swanson et al., 1999). There is no authoritative literature information on the correlation of dose or plasma concentration with clinical effects of methylphenidate. The development of tolerance indicates that drug effect at any point may not be a function of concentration alone. Additional parameters such as partial AUCs may be necessary to document bioequivalence in this case.

Several methylphenidate MR products have been approved for marketing, including Concerta (OROS), Metadate CD, Metadate ER, Ritalin LA and Ritalin SR. All formulations are therapeutically effective based on clinical trials and their unique individual shapes of the respective plasma concentration–time profile. These MR products have been clinically effective because they possess the following three essential properties: (a) avoidance of tolerance, (b) rapid onset of action, and (c) longer duration of effect. Evaluation of early exposure from the plasma profile (partial AUC) will be important for multi-source products of these brand methylphenidate products. To set bioequivalence limits on partial AUC, there is a need to evaluate carefully the within-subject variance associated with this parameter.

A.3. Zolpidem tartrate extended release products

Zolpidem is a non-benzodiazepine sedative hypnotic. The IR formulation of zolpidem (Ambien CR) was indicated for short-term treatment of insomnia characterized by difficulties with sleep initiation. The extended release formulation (Ambien CR) offers additional advantages of treating difficulties associated with sleep maintenance and producing no residual effects after wake-up. The current formulation of Ambien CR was selected based on the results of a double-blind, placebo-controlled, 10-way crossover study where eight zolpidem formulations comprising different proportions of IR and extended release were compared with zolpidem IR and placebo using pharmacodynamic endpoints (Hindmarch et al., 2004). The study revealed differential effects among formulations on awakening as well as correlations between residual effects and plasma concentrations. An in vitro–in vivo correlation (IVIVC, Level A) was established between in vitro dissolution and pharmacokinetic profile of the final formulation chosen for marketing. A clinical trial was also conducted to confirm the efficacy and

safety of the final formulation (Roth et al., 2006). In view of the essential properties of Ambien CR, FDA has recently suggested additional metrics (partial AUCs) to ensure bioequivalence of zolpidem extended release products (U.S. Department of Health and Human Services, 2007). The cutoff points for these partial AUCs will be determined pending further review of available data.

References

- Davidson, J., 1989. Seizures and bupropion: a review. *J. Clin. Psychiatry* 50, 256–261.
- Hindmarch, I., Legangneux, E., Stanley, N., 2004. A randomized double-blind, placebo-controlled, 10-way cross-over study shows that a new zolpidem modified-release formulation improves sleep maintenance compared to standard zolpidem. *Sleep* 27, A55.
- Preskorn, S.H., 1991. Should bupropion dosage be adjusted based upon therapeutic drug monitoring? *Psychopharmacol. Bull.* 27, 637–643.
- Roth, T., Soubrane, C., Titeux, L., Walsh, J.K., 2006. Efficacy and safety of zolpidem-MR: a double-blind, placebo-controlled study in adults with primary insomnia. *Sleep Med.* 7, 397–406.
- Swanson, J., Gupta, S., Guinta, D., Flynn, D., Agler, D., Lerner, M., Williams, L., Shoulson, I., Wigal, S., 1999. Acute tolerance to methylphenidate in the treatment of attention deficit hypersensitivity disorder in children. *Clin. Pharmacol. Ther.* 66, 295–305.
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science, Office of Generic Drugs, 2010. Electronic Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. <<http://www.fda.gov/cder/ob/default.htm>> (accessed 26.2.10.).
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 2000. Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. <<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf>> (accessed 26.2.10.).
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 2009. Guidance for Industry: Q8(R2) Pharmaceutical Development. <<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073507.pdf>> (accessed 26.2.10.).
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 2003. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. <<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf>>. (accessed 26.2.10.).
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 2007. Individual Product Bioequivalence Recommendation – Zolpidem. <<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175029.pdf>> (accessed 26.2.10.). In: Draft Guidance for Industry: Bioequivalence Recommendations for Specific Products. <<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072872.pdf>> (accessed 26.2.10.).
- U.S. Food and Drug Administration, 2009a. Title 21 Code of Federal Regulations (CFR) Part 320.25(f). Office of Federal Register, National Archives and Records Administration, U.S. Government Printing Office, Washington, DC.
- U.S. Food and Drug Administration, 2009b. Title 21 Code of Federal Regulations (CFR) Part 320.1. Office of Federal Register, National Archives and Records Administration, U.S. Government Printing Office, Washington, DC.
- U.S. Food and Drug Administration, 2009c. Title 21 Code of Federal Regulations (CFR) Part 320.24(b). Office of Federal Register, National Archives and Records Administration, U.S. Government Printing Office, Washington, DC.
- U.S. Food and Drug Administration, 2009d. Title 21 Code of Federal Regulations (CFR) Part 320.23(b). Office of Federal Register, National Archives and Records Administration, U.S. Government Printing Office, Washington, DC.