Generic Drug Product Development

Bioequivalence Issues

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Pharmaceutical Alternatives: Considerations for Generic Substitution

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INTRODUCTION

The issue of interchangeability/switchability relating to pharmaceutical alternatives is a controversial one and poses a challenge to regulatory authorities in particular where the consideration of generic substitution is important (1). The term *pharmaceutical alternative* as defined in the EU guideline (2) is used to define pharmaceutical products that have the same active moiety but that may differ in chemical form (i.e., salt, ester etc.) of that active compound or in dosage form or strength. A similar definition exists in the text "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) published by the Food and Drug Administration (FDA) (3). While both the European Agency for the Evaluation of Medicinal Products (EMEA) and the FDA recognize the concept that pharmaceutical alternatives may be shown to be bioequivalent, the Orange Book (3) clearly states that only *therapeutic equivalents* that are *pharmaceutical equivalents* can be considered substitutable, whereas the EMEA

Different salt forms of a particular API may differ substantially in their physicochemical properties, in particular solubility, hygroscopicity, stability, flowability, etc. In addition, the presence of impurities associated either with the route of synthesis of that particular salt or resulting as a consequence of instability and the formation of degradation products, can impart toxicity and/or undesirable biological activity quite different from the intended clinical use of the drug (11,12). Consequently, the use of one salt form of an API as opposed to another may result in a substantial difference in therapeutic efficacy with a resultant negative impact on the safety and/or quality of that specific molecule. There is no reliable way of predicting the influence of a particular salt species on the behavior of a parent compound in different dosage forms.

The selection of an appropriate form of an API is not only an important factor in the early stages of new drug product development (13) but is also a critical factor in the development of generic drug products. An interesting case is illustrated by the example of amlodipine. Amlodipine, a calcium channel blocker is marketed by Pfizer as a besylate salt and is commercially available as (Norvasc®). The original patent held by Pfizer on amlodipine besylate expired in 2003 but was extended until 2007 to compensate for a lengthy review process by the FDA (14). The original patent granted to the manufacturer protected both the chemical structure of amlodipine besylate and a series of other salts of amlodipine. A maleate salt product of amlodipine that was developed by Dr. Reddy's Laboratories Limited (AmVaz™, Reddy Pharmaceuticals Inc.) was subsequently proved to be bioequivalent to Norvasc (15). Dr. Reddy's Laboratories claimed that Pfizer's patent extension did not apply to their version of the drug, i.e., amlodipine maleate. However, on February 27, 2004, The United States Court of Appeals for the Federal Circuit reversed an earlier New Jersey District Court's dismissal of Pfizer's patent infringement action against Dr. Reddy's Laboratories' generic version of Norvasc effectively preventing a generic version of amlodipine from entering the market (16).

Apart from the legal issues, an important question to be answered is: what experiments and tests are required to ensure that a drug product containing a specific salt form of an API has comparable pharmacokinetic, pharmacologic, toxicologic and safety profiles as the registered product containing an alternative salt form of the same active substance? Furthermore, what is the likelihood that pharmaceutical alternatives, which have been shown to be bioequivalent, will have different clinical safety and efficacy profiles?

As mentioned previously, different salt forms of an API may vary in their physicochemical characteristics including but not limited to solubility and hygroscopicity. Increased hygroscopicity may reduce the stability of an API even in a pharmaceutical dosage form such as tablets, in particular if the API is susceptible to hydrolytic degradation. Furthermore, thermal

The scientific literature is replete with reports showing that the aqueous solubility of an API can be significantly modified by use of alternate salt forms of the same active moiety and that the solubilities of the different salt forms can be vastly different. The antidepressant, trazadone, for example, is currently marketed as the hydrochloride salt. In order to prepare a form of trazadone with lower aqueous solubility than the hydrochloride salt, a number of alternative salts have been prepared (18). Of the salts selected for evaluation, the tosylate and pamoate salts were found to be less water-soluble than the sulfate and hydrochloride salts and the most interesting solubility profile with values ranging from 3 mg/mL at pH 1.0 to 0.2 mg/mL at pH 12.0 was exhibited by the tosylate salt. The low aqueous solubility makes the tosylate salt the candidate of choice for the development of a prolonged release oral product for the elderly due to the potential for improved compliance in these patients. The significantly lower (8–10 fold in the pH range 1–5) solubility of the tosylate salt compared to the hydrochloride salt, may result in dissolution rate-limited absorption of trazodone following oral administration of the tosylate salt in vivo. The vast difference in solubility makes it highly unlikely that the two salts can be bioequivalent.

The impact of a difference in aqueous solubility of a specific salt on the therapeutic activity and duration of action of an API is further elucidated by evaluation of the solubility of the hydrochloride and napsylate salts of dextropropoxyphene. Dextropropoxyphene hydrochloride is highly soluble (1 in 0.3 parts water) whereas the napsylate salt is practically insoluble (1 in > 10,000 parts of water) (19). The more extensive analgesic activity and longer duration of action of the hydrochloride salt of dextropropoxyphene compared to the napsylate salt may in part be explained by the differences in solubility of the two salts (20). Furthermore the higher acute toxicity of dextropropoxyphene following administration of the hydrochloride salt compared to the napsylate salt following oral administration to mice is probably due to the faster absorption rate of the hydrochloride salt from the gastrointestinal tract (21).

Bioequivalence studies in humans in which different salt forms of basic drugs have been reported are rather limited and interestingly, none of them have reported significant differences in bioavailability between the different salt forms as a consequence of differences in their aqueous solubilities (22). For example, no enhancement in bioavailability was reported when salts of a basic antihypertensive agent with significantly different intrinsic dissolution rates were compared (23). Walmsley et al. reported no differences in the extent of bioavailability between the oxalate and citrate salts of naftidrofuryl (24) and Jamuludin et al. reported no significant differences in C_{max}, T_{max}, or AUC of quinine following oral administration of the hydrochloride, sulfate, and ethyl carbonate salts to healthy volunteers (25).

formation of these impurities resulting in the production of potentially unsafe dosage forms. Mesylate esters are known to be potent mutagenic, carcinogenic and teratogenic compounds (32,33). Therefore it can be concluded that when routes of synthesis to manufacture and prepare different salt forms of the same API result in different chemical by-products, the toxic potential of these impurities should be evaluated by preclinical testing for each salt form synthesized/prepared.

In addition to issues of safety and toxicity, the tolerability of an API may also be affected by the specific salt form of an active substance administered by specific routes of administration. The potential of an API to cause gastrointestinal irritation and/or ulceration, for example, may in part be dependent on the aqueous solubility and dissolution rate of different salt forms of that API administered via the oral route.

For example the ulcerogenic effects of five different salts of alprenolol were compared to a placebo in a porcine esophageal test model (34). The highly water soluble hydrochloride and fumarate salts of alprenolol gave rise to the highest plasma concentrations of API yet evoked serious oesophageal lesions, while the salts with low solubility, the benzoate, maleate and sebacate salts produced no irritant effects on the esophagus. Furthermore the plasma levels of alprenolol were much higher after administration of alprenolol hydrochloride in the esophagus than after an identical intraduodenal dose of the same salt possibly due the avoidance of hepatic first-pass metabolism/degradation following oesophageal absorption.

The solid-state properties of a molecule, as well as its properties in solution, can be modified by use of salt formation. The selection of a salt suitable for a specific route of administration or a particular dosage form of a drug substance requires that all relevant solid-state properties of a salt candidate be thoroughly investigated prior to the continuation of product development.

Polymorphism is frequently a critical point in determining the preference for one salt or another (9,13). Polymorphism is defined as the ability of a drug substance to exist as two or more crystalline phases that have distinct molecular structures and/or conformations of the molecules in the crystal lattice. Polymorphism is a widespread phenomenon observed in over 60% of all API's and the most critical issue related to polymorphism of an API is the equilibrium solubility which is an important determinant of dissolution rate and which in turn may affect the bioavailability of the active substance particularly following oral administration (35).

There are numerous examples where polymorphism has been associated with differences in the oral bioavailability of an active substance from solid dosage forms, including chloramphenicol palmitate and carbamazepine base (36,37). Consequently it is essential that the production of different salts in order to overcome solubility and other challenges must necessarily involve an investigation into the formation of polymorphic

Nasogastric tubes for the delivery of crushed tablets usually intended for oral administration are often used in hospitals and home care environments. In order to determine whether this alternate route of administration and essentially administration of a pharmaceutical alternate dosage form would produce equivalent responses, the antibiotic, trovafloxacin, was administered to 24 healthy volunteers in a four-period, four-treatment crossover study (40). The primary purpose of the study was to assess whether the use of an enteral feeding solution and location of the nasogastric tubes affected bioavailability of the antibiotic. The subjects were administered either two 100 mg tablets orally, two crushed tablets (pharmaceutical alternative) suspended in water via a nasogastric tube into the stomach, two crushed tablets suspended in water into the duodenum or two crushed tablets suspended in water and administered simultaneously with an enteral feeding solution into the stomach. The study in fact deals with two issues that are related to differences in route of administration and the administration of a pharmaceutical alternative dosage form in the form of crushed tablets. The results indicated that the treatment in which crushed trovafloxacin tablets were administered into the duodenum revealed bioinequivalence whereas delivery of the same pharmaceutical alternative via nasogastric tube into the stomach proved to be bioequivalent to the orally administered tablets (40).

A further illustration of bioequivalence between two different dosage forms has been recorded following the administration of 60 mg of citalopram to 24 subjects of mixed sex, the 90% CI for AUC_{last} and C_{max} were found to fall within the conventional limits for bioequivalence indicating that the two formulations can be considered bioequivalent (41).

Plasma levels of nizatidine administered to 24 healthy adult subjects and delivered from a commercial oral syrup formulation and two extemporaneously prepared liquid formulations in apple juice and infant formula were compared to those obtained following administration of a nizatidine capsule (42). The results indicated that the commercial oral syrup and extemporaneous infant formula liquid dosage form (pharmaceutical alternatives) were bioequivalent to the reference capsule using a conventional 90% CI for AUC_{last} and C_{max} whereas a possible food effect was observed for the extemporaneous apple juice formulation resulting in bioinequivalence in that comparison.

Plasma levels of levetiracetam were compared following administration of a 10% levetiracetam (750 mg) oral solution and 750 mg tablets in a crossover study in 24 healthy subjects and these two pharmaceutical alternative products were found to be bioequivalent (43).

A new rapidly disintegrating cisapride (Propulsid Quicksolv) formulation was compared to conventional cisapride (Propsulsid) tablets in 36 elderly volunteers in a crossover study and found to be bioequivalent with both AUC_{last} and C_{max} ratios falling within the established limits for

formulation principles in which succinate salt containing beads were included into a disintegrating tablet whereas the fumurate salt was included in the nondisintegrating OROS® system. The products were found to be bioequivalent using a 90% CI of 0.8 to 1.25 for both C_{max} and AUC although the variability associated with the multiple-unit system was lower than with the single-unit device (47).

The example described above demonstrates a pharmaceutical alternative, which both involves different salts in addition to different dosage forms and yet was shown to be bioequivalent.

DIFFERENT ROUTES OF ADMINISTRATION

It is well known that the route of administration and type of delivery system may impact on bioavailability and hence pharmaceutical alternatives intended for a different route of administration compared to the reference product are quite unlikely to be shown to be bioequivalent.

An interesting case involves the bioavailability and bioequivalence of the same dose of etodolac administered as either a tablet or a suppository formulation in healthy volunteers of both sexes. In a crossover design when these different dosage forms were compared, their AUC_{last} values were found to be within the bioequivalence acceptance range for that parameter but not their C_{max} values (48), hence bioequivalence cannot be claimed.

A further example that demonstrates the importance of considering differences between routes of administration for the same product can be gleaned from the following. When hydroxylpropyl methylcellulose or gelatine capsules containing ibuprofen, i.e., two pharmaceutical alternatives intended for oral administration, were administered rectally, there were significant differences in bioavailability between these formulations indicating bioinequivalence. However when the same capsules were administered orally in a crossover study the products were found to be bioequivalent (49). The two capsule formulations are by definition not pharmaceutical alternatives but rather pharmaceutical equivalents and would be substitutable when administered orally but not rectally. Clearly in this case the impact of excipients on drug release with specific routes of administration is evident.

Consequently the use of bioequivalent pharmaceutically equivalent products should only be considered substitutable provided the same route of administration is used.

The definition of a pharmaceutical equivalent clearly states that such dosage forms must be formulated for delivery via the same route of administration as well as the other considerations including amount and type of active moiety. However the definition of pharmaceutical alternative dosage forms makes no reference to the route of administration and also provides for different strengths, different salts of active moieties and different dosage forms.

2. EMEA. Note for Guidance on the Investigation of Bioavailability and Bioequivalence for Proprietary Medicinal Products (CPMP). European Agency for the Evaluation of Medicinal Products, London, UK, 2001.
3. Orange Book. Approved Drug Product with Therapeutic Equivalence Evaluations, 24th Edition, Food and Drug Administration, USA, 2004.
4. FDA. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations. Center for Drug Evaluation Research, Food and Drug Administration, WA, USA, 2000.
5. Berge SM, Bighley LD, Monkhouse DC. Pharmaceutical salts. J. Pharm Sci 1977; 66:1–19.
6. Gould PL, Salt selection for basic drugs. Int J Pharm 1986; 33:201—17.
7. Davies G, Changing the salt, changing the drug. The PharmJ 2001; 266: 322—3.
8. Stahl H, Wermuth CG (eds.). Handbook of Pharmaceutical Salts: Properties, Selection and Use., Weinheim: Wiley-VCH, 2002.
9. Balbach S, Korn C. Pharmaceutical evaluation of early development candidates "the 100 mg approach". Int J Pharm 2004; 275:1–12.
10. Gardner CR, Almarsson O, Chen H, et al. Application of high throughput technologies to drug substance and drug product development. Comp Chem Eng 2004; 28:943–53.
11. Bastin RJ, Bowker MJ, Slater BJ. Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities. Organ Process Res Develop 2000 4: 427–35.
12. Byrn S, Pfeiffer R, Ganey M, Hoiberg C, Poochikian G. Pharmaceutical solids: a strategic approach to regulatory considerations. Pharm Res 1995; 12:945–54.
13. M.J. Bowker. A procedure for salt selection and optimisation. In: Stahl PH and Wermuth C (eds.). Handbook of Pharmaceutical Salts: Properties, Selection and Use. Weinheim: Wiley-VCH, 2002:161–189.
14. Anonymous: Court reversal in favour of Pfizer. Nature Rev Drug Discov 2004; 3:290.
15. Suh SS, Mohan MS, Davis MW. Amlodipine: pharmacokinetics of the maleate vs besylate salts. Am J Hypertens 2004; 17:P-250.
16. http://www.ll.georgetown.edu/federal/judicial/fed/opinions/03opinions/03-1227.html.
17. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res 1995; 12:413–20.
18. Ware EC, Lu DR. An automated approach to salt selection for new unique trazodone salts. Pharm Res 2004; 21:17784.
19. Moffat AC, Osselton MD and Widdop B (eds.), Clarke's Analysis of Drugs and Posions, 3rd edn. London: The Pharmaceutical Press, 2004:892–3.
20. Sunshine A, Laska E, Slafta J, Fleischman E. A comparative analgesia study of propoxyphene hydrochloride, propoxyphene napsylate, and placebo. Toxicol Appl Pharmacol 1971; 19:512–518.
21. Emmerson JL, Gibson WR, Anderson RC. Acute toxicity of propoxyphene salts. Toxicol Appl Pharmacol 1971; 19:445–51.

38. Doser K, Meyer B, Nitsche V, Binkert-Graber P. Bioequivalence evaluation of two different oral formulations of loperamide (Diarex Lactab vs Immodium capsules). Int J Clin Pharmacol Ther 1995; 33:431–6.
39. Amer A, Karol MD, Pan W-J, et al. Comparison of the pharmacokinetics of lansoprazole 15-and 30-mg sachets for suspension versus intact capsules. Clin Ther 2004; 26:2076–83.
40. Vincent J, Teng R, Pelletier SM, Willavize SA, Friedman HL. The bioavailability of nasogastric versus tablet-form oral trovafloxacin in healthy subjects. Am J Surg 1998; 176(Suppl 6A):23S–26S.
41. Gutierrex MM, Abramowitz W. Pharmacokinetic comparison of oral solution and tablet formulations of citalopram: a single-dose, randomized, crossover study. Clin Ther 2000; 22:1525–32.
42. Abdel-Rahman SM, Johnson FK, Gauthier-Dubois G, Weston IE, Kearns GL. The bioequivalence of nizatidine (Axid) in two extemporaneously and one commercially prepared oral liquid formulations compared with a capsule. J Clin Pharmacol 2003; 43:148–153.
43. Coupez R, Straetemans R, Sehgal G, Stockis A, Lu Z. Levetiracetam: relative bioavailability and bioquivalence of a 10% oral solution (750 mg) and 750-mg tablets. J Clin Pharmacol 2003; 43:1370–6.
44. Zhou H, Herron J, Liu Y, Lee P, Pesco-Kopowitz L. A new rapidly disintegrating formulation of cisapride is bioequivalent to standard cisapride tablets in then elderly. Clin Drug Invest 1997; 14:487—493.
45. Van Den Heuvel MW, Kleijn HJ, Peeters PAM. Bioequivalence trial of orally distintegrating mirtazapine tablets and conventional oral mirtazapine tablets in healthy volunteers. Clin Drug Invest 2001; 21:437–442.
46. Dulac O, Alvarez J-C. Bioequivalence of a new sustained-release formulation of sodium valproate, valproate modified release granules, compared with existing sustained-release formulations after once-or twice daily administration. Pharmacotherapy 2005; 25:35–41.
47. Sandberg A, Abrahamsson B, Svenheden A, Olofsson B, Bergtrand R. Steady-state bioavailability and day-to-day variability of a multiple-unit (CR/ZOK) and a single-unit (OROS) delivery system of metoprolol after once-daily dosing. Pharm Res 1993; 10:28–34.
48. Molina Martinez IT, Herrero R, Gutierrez JA, Iglesias JM, Fabregas JL, Martinez-Tobed A, Cadorniga R. Bioavailability and bioequivalence of two formulations of etodolac (tablets and suppositories). J Pharm Sci 1997; 82: 211–13.
49. Honkanen O, Seppa H, Eerikainen S, Tuominen R, Marvola M. Bioavailability of ibuprofen from orally and rectally administered hydroxypropyl methyl cellulose capsules compared to corresponding gelatine capsules. S.T.P. Pharma Sci 2001; 11:181–185.
50. Uemura N, Onishi T, Mitaniyama A, et al. Bioequivalence and rapid absorption of zolmitriptan nasal spray compared with oral tablets in healthy Japanese subjects. Clin. Drug Invest 2005; 25:199–208.