Generic substitution: The use of medicinal products containing different salts and implications for safety and efficacy

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Abstract

In their quest to gain early entry of new generic products into the market prior to patent expiration, one of the strategies pursued by generic drug product manufacturers is to incorporate different salts of an approved active pharmaceutical ingredient (API) in a brand company's marketed dosage form and subject such dosage forms to bioequivalence assessment. These initiatives present challenges to regulatory authorities where the decision to approve bioequivalent products containing such pharmaceutical alternatives must be considered in the light of safety and efficacy, and more particularly, with respect to their substitutability. This article describes the various issues and contentions associated with the concept of pharmaceutical alternatives, specifically with respect to the uses of different salts and the implications for safety, efficacy and generic substitution.

1. Introduction

Most drugs are either weak organic acids or weak organic bases and can therefore exist as different salt forms. Although the active pharmaceutical ingredient (API) in these different salts is the same, each of these salts may be considered as being distinct chemical entities with their own chemical and biological profiles which may lead to differences in their clinical efficacy and safety (Berge et al., 1977, Gould, 1986, Davies, 2001 and Stahl and Wermuth, 2002a). The term *pharmaceutical alternatives* is used in relation to different salts (or esters) of the same active substance in the EU Note for Guidance as well as in the FDA Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products (EMEA, 2001 and FDA, 2000). According to the EU guidelines “medicinal products are pharmaceutical alternatives if they contain the same active moiety but differ in chemical form (salt, ester, etc.) of that moiety or in the dosage form or strength”. Similarly, the definition of

pharmaceutical alternatives as stated in the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations", 24th edition (Orange Book, 2004) is as follows: "Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths …". In contrast to the issue of pharmaceutical alternatives, the Orange Book (2004) also defines the term, pharmaceutical equivalents, as follows: "Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration. Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e. strength, quality, purity and identity), but they may differ in characteristics, such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavours and preservatives), expiration time and within certain limits, labelling".

According to both the FDA (2000) and EMEA (2001) guidelines, bioequivalence can be established between two medicinal products, which are pharmaceutical alternatives. However, the definition of therapeutic equivalence as given in the Orange Book (2004) precludes the substitutability of pharmaceutical alternatives, as follows: "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 labelling". On the other hand the European Agency for the Evaluation of Medicinal Products (EMEA) makes provision for medicinal products which are either pharmaceutically equivalent or pharmaceutical alternatives to be declared as therapeutic equivalents, as follows: "In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products which are pharmaceutically equivalent or pharmaceutical alternatives, provided they contain excipients generally recognised as not having an influence on safety and efficacy and comply with labelling requirements with respect to excipients" (EMEA, 2001). The immediately preceding paragraph in the same EMEA guideline confoundingly states that:

“A medicinal product is therapeutically equivalent with another product if it contains the same active substance or therapeutic moiety and, clinically, shows the same efficacy and safety as that product, whose efficacy and safety has been established”. The issue is complicated by incorporation of the phrase “…, clinically, shows the same efficacy and safety as that product, whose efficacy and safety has been established”, in the definition. In our view this implies that therapeutic equivalence cannot be established between pharmaceutical alternatives on bioequivalence data alone. Hence, whereas pharmaceutically equivalent products can clearly be considered therapeutically equivalent based on a bioequivalence study, additional preclinical and/or clinical data may be required for a pharmaceutical alternative to be considered therapeutically equivalent.

In this commentary, scientific facts/data will be presented to show that establishing bioequivalence between oral drug products containing different salts of the same active substance, will usually not suffice to claim therapeutic equivalence and consequently substitutability/interchangeability.

2. Active pharmaceutical ingredients and their salts

Converting an API to a particular salt form is a means of modifying and sometimes optimising its physicochemical properties (Stahl and Wermuth, 2002a and Stahl and Wermuth, 2002b). However, changing the salt form may also affect the biological properties of the drug and have significant implications for safety and toxicity (Davies, 2001). The most appropriate salt form of an active moiety should ideally be selected at an early stage of the development of a New Chemical Entity (NCE) to optimise the characteristics of the final formulation. Indeed, different salt forms of a particular API can differ markedly in physicochemical properties, such as 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 drug's intended clinical use (Bastin et al., 2000 and Byrn et al., 1995). Hence, it may therefore be possible that substitution of one salt form of an API for another can alter therapeutic efficacy, safety and/or quality. Unfortunately, there

is no reliable way of predicting the influence of a particular salt species on the behaviour of the parent compound in dosage forms.

It is estimated that half of all the active substances used in medicinal therapy are administered as salts, and salification of a drug substance has become an essential step in drug development (Balbach and Korn, 2004 and Gardner et al., 2004). Selecting an appropriate salt form of an API is not only an important consideration in the early stages of new drug development (Bowker, 2002), it may also play a role in the development of generic drug products as illustrated by the example of amlodipine. This calcium channel blocker is marketed by Pfizer as the besylate salt (Norvasc®). Pfizer's original patent on amlodipine besylate expired in 2003 but was extended until 2007 to compensate for a lengthy review process by the FDA (Anon., 2004). Pfizer's original patent attempted to protect both the chemical structure of amlodipine besylate and a series of other salts of amlodipine. Dr. Reddy's Laboratories Limited developed a generic version of amlodipine in the form of the maleate salt and showed that their product (AmVaz™, Reddy Pharmaceuticals Inc.) was bioequivalent to Pfizer's Norvasc® (Suh et al., 2004). Dr. Reddy's Laboratories tried to obtain marketing authorization arguing 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 the earlier New Jersey District Court's dismissal of Pfizer's patent infringement action against Dr. Reddy's Laboratories' generic version of Norvasc®, thus effectively preventing the generic version from entering the market (Anon.: Pfizer Inc. versus Dr. Reddy's Laboratories, www.ll.georgetown.edu/federal/judicial/fed/opinions/03opinions/03-1227.html, visited 05/23/05). A short discussion of the properties of amlodipine maleate, with particular emphasis on stability and subsequent effects on efficacy and safety is presented in Section 3.4 (vide infra).

Apart from the legal issues, the 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, pharmacological, toxicological 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?

3. Development of generic drug products using an alternative salt of the same active moiety

The following issues are important when considering whether alternative salt forms of the same active moiety can be considered therapeutically equivalent and hence have to be addressed when developing a generic drug product using an alternative salt form of the active substance.

3.1. Solubility, dissolution and bioavailability

Many examples can be found in the scientific literature showing that the water solubilities of alternative salt forms of the same active moiety can be quite different. The antidepressant, trazodone, for example, is currently marketed as the hydrochloride salt. Ware and Lu (2004) prepared a number of alternative salts in an attempt to find a salt form of trazodone with lower aqueous solubility compared to trazodone hydrochloride. Among the salts selected for final evaluation, the tosylate and pamoate salts of trazodone were less water-soluble than the sulphate and hydrochloride salts. The tosylate salt showed 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. This characteristic makes it the best candidate, compared to the other salts, for the development of a prolonged release oral trazodone product to improve patient compliance in the elderly. Because of the significantly lower (8–10-fold in the pH range 1–5) solubility of the tosylate salt compared to the marketed hydrochloride salt, the in vivo absorption rate of trazodone following oral administration of the tosylate salt may be significantly lower. Consequently, the two salts will probably be neither bioequivalent, i.e. having a similar rate and extent of absorption, nor therapeutically equivalent.

Following oral administration as a solid dosage form, the dissolution rate of the active substance in the gastrointestinal juices is affected by its aqueous solubility. Therefore, solid dosage forms containing alternative salts of the same active substance may show

different in vivo dissolution characteristics. According to the principles underlying the Biopharmaceutics Classification System, for active drug substances with a high intestinal permeability, the in vivo dissolution rate will determine the rate and in some cases also the extent of absorption (Amidon et al., 1995). For active substances with a low intestinal permeability and a relatively good aqueous solubility, however, in vivo dissolution is no longer the rate-limiting step in the absorption process and differences in aqueous solubility and dissolution are usually not important determinants of bioavailability. Human bioequivalence studies comparing salt forms of basic drugs have been rather limited and none of them have reported significant differences in bioavailability between different salt forms due to differences in their aqueous solubilities (Engel et al., 2000). Lin et al. (1972), for example, reported no enhancement in bioavailability when salts of a basic antihypertensive agent, 1-(2,3-dihydro-5-methoxybenzo[*b*]furan-2-ylmethyl)-4-(*o*-methoxyphenyl)piperazine, having significantly different intrinsic dissolution rates, were compared. Walmsley et al. (1986) also indicated that they did not observe a difference in the extent of bioavailability between oxalate and citrate salts of naftidrofuryl, while Jamuludin et al. (1988) saw no significant differences in C_{max}, T_{max}, or AUC of quinine following oral administration of the hydrochloride, sulphate and ethyl carbonate salts of this antimalarial to healthy volunteers. Consequently, it may be concluded that an in vivo bioequivalence study is absolutely necessary if therapeutic equivalence between alternative salts of the same active drug molecule is being claimed, except when both salts are highly soluble and highly permeable, i.e. BCS class I compounds. In that case a BCS-based waiver for an in vivo BE study for an immediate release oral dosage form which exhibits rapid in vitro dissolution can be requested, provided a number of additional conditions are met (FDA, 2000).

3.2. Toxicity

Toxicity associated with the salt of an active drug molecule may be due to the conjugate anion or cation used to form the salt (Berge et al., 1977 and Stahl and Wermuth, 2002b). For example, the nephrotoxicity of pravadoline maleate, which was reported to cause renal tubular lesions in the dog, has been shown to be the result of the formation of maleic acid from the maleate anion (Everett et al., 1993). The need to evaluate the safety

profile of the salt-forming agent depends largely on its chemical nature, its biological characteristics, whether the agent has been used in other medicinal products, foods and beverages or not, as well as the relative ratio of the salt-forming component to the active substance. Toxicity studies are required for a new salt form of an active substance when the salt of that active substance has been prepared by using a new salt-forming agent with little or no information on its toxicity profile. Toxicity studies on the salt-forming agent alone are also necessary. Monographs on 68 salt-forming acids and 27 salt-forming bases have been published in the *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, edited by Stahl and Wermuth (2002a) as well as a comprehensive list of salt-forming acids and bases with information regarding their safety/toxicity (Stahl and Wermuth, 2002b and Wermuth, 2002).

Potentially toxic chemical impurities formed during the preparation of a specific salt of an API may also explain differences found in the toxicity profiles of various salt forms of an active drug molecule. It is therefore necessary to evaluate the toxic potential of all impurities found during the synthesis of a specific salt form (Bauer et al., 1998). For example, methane sulfonic acid is used in the formation of methane sulfonates (also called mesylate salts) of active basic drug molecules, such as pergolide, nelfinavir, imatinib and amlodipine. Benzene and toluene sulfonates (besylates and tosylates, respectively), have also been prepared. Recently, the potential health hazards of trace amounts of mesylate esters, including methyl methanesulfonate, ethyl methanesulfonate and isopropyl methanesulfonate, in pharmaceuticals have attracted the attention of health authorities (Anon., 2000). These impurities could arise from the reaction of methane sulfonic acid with solvents, such as methanol, ethanol and isopropyl alcohol during the manufacture of the mesylate salts of active substances. These mesylate esters are known to be potent mutagenic, carcinogenic and teratogenic compounds (Sega et al., 1986 and Morris et al., 1994). In general, it can be concluded that when the routes to synthesize or prepare alternative salt forms of the same active moiety result in different chemical by-products, the toxic potential of these impurities should be evaluated by preclinical testing for each salt form synthesized/prepared.

The specific salt form of an active substance may also affect tolerability. Gastrointestinal irritation and ulceration, for example, may be dependent upon the aqueous solubility and dissolution rate of different salt forms administered by the oral route. Olovson et al. (1986) tested the ulcerogenic effect of five different salts of alprenolol against placebo in a porcine oesophageal test model. The salts with high water solubility, such as the hydrochloride and the fumarate, gave rise to the highest plasma concentrations of alprenolol and evoked serious oesophageal lesions, while the salts with low solubility – the benzoate, maleate and sebacate – had no irritant effect on the oesophagus. The plasma levels of alprenolol were much higher following administration of alprenolol hydrochloride in the oesophagus than after an identical intraduodenal dose of the same salt possibly because of the avoidance of first-pass metabolism during oesophageal absorption.

3.3. Polymorphism

The solid-state properties of a molecule, as well as its properties in solution, can be modified by salt formation. Selecting a salt suitable for a certain route of administration or a particular dosage form of a drug substance requires that all the relevant solid-state properties of the salt candidates be thoroughly investigated. Polymorphism is frequently a critical point in determining preferences for one salt or another (Balbach and Korn, 2004 and Bowker, 2002). Polymorphism can be defined as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Polymorphism is a widespread phenomenon observed in more than half of all active drug substances. The most critical issue related to drug substance polymorphism is equilibrium solubility which is an important determinant of dissolution rate and which may affect the bioavailability following oral administration of the active substance (Huang and Tong, 2004). Clearly, if polymorphism has an effect on the bioavailability of a drug substance, a bioequivalence study between two formulations containing different polymorphs of the same drug should reveal those effects.

3.4. Stability and formulation/production considerations

As mentioned before, the different salt forms of an active drug moiety can vary in a number of physicochemical characteristics including hygroscopicity. Increased hygroscopicity may reduce stability of the active drug moiety, even in a pharmaceutical dosage form, such as tablets, especially when the active drug moiety is susceptible to hydrolytic degradation. In addition, thermal stability and degradation pathways may be different for alternative salt forms of the same active moiety possibly requiring the need to evaluate new degradation products by using appropriate toxicological studies.

Amlodipine maleate provides an interesting example where instability of this particular salt results in the formation of a degradation product, which has significant implications for safety and toxicity. The maleate salt of amlodipine, unlike the besylate salt, suffers from intrinsic chemical instability which results in the formation of *N*-(2-{[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydro-2-pyridyl]methoxy}ethyl) aspartic acid, an impurity with demonstrated biological activity. It is formed by an intramolecular reaction of the unsaturated maleic acid with the primary amine group of amlodipine. This compound has been shown to possess a distinctly different biological profile to amlodipine itself (Amlodipine Citizen Petition, http://www.fda.gov/ohrms/dockets/dailys/03/Sept03/090303/03p-0408-cp00001-08-Tab-G-vol3.pdf, visited 05/23/05). Hence, the maleate salt of amlodipine cannot be considered to be therapeutically equivalent to the besylate salt since the latter does not have this additional clinical effect. The consequences of the presence of the biologically active impurity associated with amlodipine maleate therefore militates against generic substitution between maleate and besylate salts even if bioequivalence can be demonstrated. Whereas low levels of this impurity may not result in serious clinical consequences, the instability of the amlodipine maleate salt suggests that relatively high levels would likely result following the manufacture of dosage forms and on prolonged storage. However, a case could be made to suggest interchangeability and thus permit generic substitution if a stabilised formulation of amlodipine maleate is used to show bioequivalence between the maleate and besylate salts. Such stabilized formulations have

been described in a recent patent (Bilotte et al., 2002) where it is claimed that the formation of amlodipine aspartate can be prevented.

The choice of a particular salt form can have a profound effect on the physicochemical properties, which are critical for the optimal formulation of the dosage form and large-scale manufacturing. The melting point of a particular salt often plays an important role. Generally, drugs with low melting points exhibit plastic deformation which can result in caking and aggregation of the API which can alter flow properties and compression characteristics and subsequently impact negatively on dose uniformity, friability, disintegration and dissolution rate of solid dosage forms. The formation of plastic materials can create problems for size reduction and tablet processing due to melting and deposition of drug on milling equipment and film formation on tabletting punches with deleterious consequences for the bulk manufacture of tablets (Florence and Attwood, 1988).

4. Regulatory requirements

The health authorities of the European Union as well as those of the USA consider alternative salts of approved drug substances as NCEs (Asche et al., 2002). However, the application to register medicinal products containing an alternative salt of an approved active substance as a generic product may be facilitated, under certain conditions, by the use of previous knowledge on and clinical experience gained with the active moiety approved as a different salt form. Therefore, in many cases of salt changes or development of a generic drug product on the basis of an alternative salt form of the active moiety already marketed, an abbreviated or abridged application may be submitted as long as evidence can be provided that the alternative salt form does not lead to a change in the pharmacokinetics of the active moiety, nor in its pharmacodynamic and/or toxicity characteristics, which could change the safety/efficacy profile. Notwithstanding the above, in the USA, pharmaceutical alternatives which have been shown to be bioequivalent to an approved reference product containing a different salt and/or dosage form, would not be considered to be therapeutically equivalent and generic substitution of such products is therefore not permitted.

5. Conclusions

According to the CPMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence, demonstration of bioequivalence is the most appropriate method of substantiating therapeutic equivalence between medicinal products which are pharmaceutically equivalent or pharmaceutical alternatives, such as different salt forms of the same active moiety (EMEA, 2001). If bioequivalence between two different salts of the same active moiety has been demonstrated, it is clear that any differences in physicochemical properties, such as solubility, between the two salts do not have any significant effect on the in vivo bioavailability of the active moiety. However, this does not suffice to conclude that these alternative salt forms are therapeutically equivalent. Therapeutic equivalence between two medicinal products not only implies the same efficacy but also the same safety profile. The issues raised above related to the possible difference in toxicity and stability of two different salt forms of the same active moiety, demonstrate that an alternative salt form may have to undergo toxicological evaluation, in addition to a valid BE study showing in vivo bioequivalence, before therapeutic equivalence, for example, to a different (marketed) salt form of the same active moiety, can be accepted.

References

1. Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability (1995) Pharmaceutical Research, 12 (3), pp. 413-420.

2. Alkyl mesylate (methanesulphonate) impurities in mesilate salts (2000) Pharmeuropa, 12, p. 27.

3. Court reversal in favour of Pfizer (2004) Nature Reviews Drug Discovery, 3 (4), p. 290.

4. Asche, H., Kondo, J.-I., Ajayi, F.O. Regulatory aspects of drug salts (2002) Handbook of Pharmaceutical Salts: Properties, Selection and Use, pp. 237-247. P.H. Stahl C.G. Wermuth Wiley-VCH Winheim

5. Balbach, S., Korn, C. Pharmaceutical evaluation of early development candidates "the 100 mg-approach" (2004) International Journal of Pharmaceutics, 275 (1-2), pp. 1-12.

6. Bastin, R.J., Bowker, M.J., Slater, B.J. Salt selection and optimisation procedures for pharmaceutical new chemical entities (2000) Organic Process Research and Development, 4 (5), pp. 427-435.

7. Bauer, M., De Leede, L., Van Der Waart, M. Purity as an issue in pharmaceutical research and development (1998) European Journal of Pharmaceutical Sciences, 6 (4), pp. 331-335.

8. Berge, S.M., Bighley, L.D., Monkhouse, D.C. Pharmaceutical salts (1977) Journal of Pharmaceutical Sciences, 66 (1), pp. 1-19.

9. Bilotte, A., Pavitt, S., Pettman, A.J., Smith, Z.E.F. (2002) Stabilized Amlodipine Maleate Formulations. Pfizer Ltd., European Patent No. EP1266654.

10. Bowker, M.J. A procedure for salt selection and optimisation (2002) Handbook of Pharmaceutical Salts: Properties, Selection and Use, pp. 161-189. P.H. Stahl C.G. Wermuth Wiley-VCH Winheim

11. Byrn, S., Pfeiffer, L.R., Ganey, L.M., Hoiberg, C., Poochikian, G. Pharmaceutical solids: A strategic approach to regulatory considerations (1995) Pharmaceutical Research, 12 (7), pp. 945-954.

12. Davies, G. Changing the salt, changing the drug (2001) Pharmaceutical Journal, 266 (7138), pp. 322-323.

13. Emea (2001) Note for Guidance on the Investigation of Bioavailability and Bioequivalence, Committee for Proprietary Medicinal Products (CPMP) European Agency for the Evaluation of Medicinal Products London, UK

14. Engel, G.L., Farid, N.A., Faul, M.M., Richardson, L.A., Winneroski, L.L. Salt form selection and characterization of LY333531 mesylate monohydrate (2000) International Journal of Pharmaceutics, 198 (2), pp. 239-247.

15. Everett, R.M., Descotes, G., Rollin, M., Greener, Y., Bradford, J.C., Benziger, D.P., Ward, S.J. Nephrotoxicity of pravadoline maleate (WIN 48098-6) in dogs: Evidence of maleic acid-induced acute tubular necrosis (1993) Fundamental and Applied Toxicology, 21 (1), pp. 59-65.

16. Fda (2000) 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

17. Florence, A.T., Attwood, D. (1988) Physicochemical Principles of Pharmacy. second ed. Macmillan Press London

18. Gardner, C.R., Almarsson, O., Chen, H., Morissette, S., Peterson, M., Zhang, Z., Wang, S., (...), Cima, M. Application of high throughput technologies to drug substance and drug product development (2004) Computers and Chemical Engineering, 28 (6-7), pp. 943-953.

19. Gould, P.L. Salt selection for basic drugs (1986) International Journal of Pharmaceutics, 33 (1-3), pp. 201-217.

20. Huang, L.-F., Tong, W.-Q. Impact of solid state properties on developability assessment of drug candidates (2004) Advanced Drug Delivery Reviews, 56 (3), pp. 321-334.

21. Jamaludin, A., Mohamad, M., Navaratnam, V., Selliah, K., Tan, S.C., Wernsdorfer, W.H., Yuen, K.H. Relative bioavailability of the hydrochloride, sulphate and ethyl carbonate salts of quinine (1988) British Journal of Clinical Pharmacology, 25 (2), pp. 261-263.

22. Lin, S.L., Lachman, L., Swartz, C.J., Huebner, C.F. Preformulation investigation. I. Relation of salt forms and biological activity of an experimental antihypertensive. (1972) Journal of Pharmaceutical Sciences, 61 (9), pp. 1418-1422.

23. Morris, S.M., McGarrity, L.J., Domon, O.E., Chen, J.J., Hinson, W.G., Bucci, T.J., Warbritton, A.R., (...), Casciano, D.A. The role of programmed cell death in the toxicity of the mutagens, ethyl methanesulfonate and N-ethyl-N'-nitrosourea. In AHH-1 human lymphoblastoid cells (1994) Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis, 306 (1), pp. 19-34.

24. Olovson, S.-G., Havu, N., Regardh, C.-G., Sandberg, A. Oesophageal ulcerations and plasma levels of different alprenolol salts: Potential implications for the clinic (1986) Acta Pharmacologica et Toxicologica, 58 (1), pp. 55-60.

25. Orange Book, (2004) Approved Drug Products with Therapeutic Equivalence Evaluations. 24th ed. Food and Drug Administration USA

26. Sega, G.A., Sluder, A.E., McCoy, L.S. The use of alkaline elution procedures to measure DNA damage in spermiogenic stages of mice exposed to methyl methanesulfonate (1986) Mutation Research, 159 (1-2), pp. 55-63.

27. Stahl, H., Wermuth, C.G. (2002) Handbook of Pharmaceutical Salts: Properties, Selection and Use. Wiley-VCH Weinheim

28. Stahl, P.H., Wermuth, C.G. Monographs on acids and bases (2002) Handbook of Pharmaceutical Salts: Properties, Selection and Use, pp. 265-327. P.H. Stahl C.G. Wermuth Wiley-VCH Weinheim

29. Suh, S.S., Mohan, M.S., Davis, M.W. Amlodipine: Pharmacokinetics of the maleate vs. besylate salts (2004) Am. J. Hypertens., 17, p. 250.

30. Walmsley, L.M., Taylor, T., Wilkinson, P.A. Plasma concentrations and relative bioavailability of naftidrofuryl from different salt forms (1986) Biopharmaceutics and Drug Disposition, 7 (4), pp. 327-334.

31. Ware, E.C., Lu, D.R. An Automated Approach to Salt Selection for New Unique Trazodone Salts (2004) Pharmaceutical Research, 21 (1), pp. 177-184.

32. Wermuth, C.G. Appendix (2002) Handbook of Pharmaceutical Salts: Properties, Selection and Use, pp. 329-350. P.H. Stahl C.G. Wermuth Wiley-VCH Winheim