Identical Bioequivalence?

It has been heard, with increasing frequency, from some professional pharmacists and academicians that decisions regarding bioequivalence between "identical" products will be impossible for a pharmacist to make until strict regulatory guidelines are developed. This "cookbook" approach to bioequivalency seems to me to be irrational at best and demeaning to the profession of pharmacy at worst.

Regulatory guidelines in terms of physical and biological effect characteristics of drug products, as base guidelines, could be misleading and confusing. For example, a high variation in established bioequivalency parameters might be acceptable for, for example, aspirin tablets. However, lifesaving and potentially dangerous drug forms such as digoxin tablets would require a narrower allowable variation. These variable limits would necessitate the stating of each acceptable level of variation for each stated bioequivalency parameter that would differ from drug to drug, dosage form to dosage form, and formulation to formulation.

I believe that a set of compendial or "quasicompendial" regulations or guidelines for bioequivalency determination would be needed only by the truly incompetent professional. The judgmental nature of the decision necessitates that it be made by a knowledgeable professional weighing appropriate negative and positive aspects.

For example, I can visualize several instances where valid differences in bioequivalency parameters could exist and would not preclude product selection of the "inferior" brand. What if there is a large monetary savings to the patient with little or no demonstrable compromise in therapeutic effect, as could conceivably occur with aspirin tablets USP? What if a pharmacist wants to prepare extemporaneously a potassium chloride elixir with a more palatable flavor for an individual patient rather than using a prescribed trade name product rejected by the patient on the basis of taste?

The major issue is whether compendial or regulatory agency guidelines dealing with bioequivalency remove a professional judgmental prerogative that the pharmacist only recently gained and leave in its place regulations that could confuse patients and needlessly restrict decisionmaking of highly trained professionals. I think that *informal* published guidelines (by APhA or other scientific/professional groups) would keep the pharmacist apprised of the status of bioequivalency and still maintain the prerogatives essential to a viable profession.

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New Solubility Equation

We wish to report a new approach to extend the Hildebrand–Scatchard regular solution theory[1] to include strong solvent–solute interactions of hydrogen bonding and other types.

The modified Hildebrand approach provides results over the solvent range from nonpolar to polar. The activity coefficient of the solute, to be derived in a paper under preparation, takes the form:

$$\log \alpha_2 = A(\delta_1 - \delta_2)^2 + A(2\delta_1\delta_2 - 2W) \quad \text{(Eq. 1)}$$

$$\log \alpha_2 = A(\delta_1^2 + \delta_2^2 - 2W) \quad \text{(Eq. 2)}$$

where A is a quantity from regular solution theory that includes the solvent volume fraction and the solute molar volume, W is a term for the solute–solvent interaction to account for deviations from regular solution behavior, δ_1 is the total polar–nonpolar solvent solubility parameter, and δ_2 is the nonpolar solute parameter.

The value of W in any solvent may be back-calculated using a simple computer program to solve a polynomial equation. Once W is obtained, the approximate solubility of the compound in a solvent of known solubility parameter, ranging from nonpolar hydrocarbons to alcohols, glycols, and water, may be calculated.

Table I lists solubility results for naphthalene in several solvents. The experimental data are those of Gmehling *et al.*[2]. The method yields solubilities in good correspondence with experimental results, except where unusally strong solute–solvent interactions exist.

The following example for naphthalene in ethanol demonstrates the method. With experimental solubilities, a W is obtained for solvent–solute pairs of known solubility by employing Eq. 2. The W's are regressed against a polynomial (quartic) in δ_1 for as many experimental solubilities as are available. From the data in Table I, one obtains the expression:

$$W = -344.1932 + 144.0207\delta_1 - 18.8238\delta_1^2 + 1.1250\delta_1^3 - 0.0242\delta_1^4 \quad \text{(Eq. 3)}$$

To obtain the solubility in ethanol (assumed in this sample to be unknown), one back-calculates W using an ethanol δ_1 value of 12.79 (total solubility parameter of Hoy and Martin[3]). One then obtains X_2 by the application of Eq. 4:

$$-\log X_2 = \frac{\Delta H_m^f}{2.303RT}\frac{T_m - T}{T_m} + A(\delta_1^2 + \delta_2^2 - 2W) \quad \text{(Eq. 4)}$$

The negative logarithm of the ideal solubility of naphthalene at 40° (first right-hand term of Eq. 4) is 0.3565, and A is 0.06458.

The regression in δ_1 (Eq. 3) yields a value of 124.946 for W as compared with 124.659 obtained from experimental solubility results. The solubility of naphthalene in ethanol at 40° is then obtained using the modified Hildebrand expression (Eq. 4):

$$\log X_2 = -\{0.3565 + 0.06458[(12.79)^2 + (9.89)^2 - 2(124.946)]\} \quad \text{(Eq. 5)}$$

where X_2 (calc.) = 0.080 and X_2 (exp.) = 0.073. An equation relating $\log \alpha_2/A$ and δ_1 may also be written by substituting the expression for W from Eq. 3 into Eq. 4, and one may thus obtain predicted solubilities more directly.

As a means of estimating the solubility in individual and mixed solvents, the classical Hildebrand approach has frequently been criticized for its incapacity to deal with solute–solvent interactions any stronger than van der Waals dispersion forces. This new approach handles ill-behaved systems such as ethanol–naphthalene where the

Table I—Predicted Solubilities of Naphthalene (δ_2 = 9.89) in Various Solvents at 40°

Solvent	δ_1	A	W (Eq. 2)[a]	X_2 (obs.), Ref. 2	X_2 (calc.), Eq. 4
Hexane	7.27	0.05539	72.652 (72.634)	0.222	0.221
Chloroform	9.14	0.0523	89.645 (89.781)	0.473	0.413
Acetone	9.62	0.02124	93.625 (93.613)	0.378	0.378
Cyclohexanol	10.92	0.04847	105.527 (104.773)	0.225	0.190
Isopropanol	11.50	0.06867	109.476 (110.453)	0.076	0.103
n-Butanol	11.60	0.06353	111.629 (111.486)	0.116	0.111
n-Propanol	12.18	0.06417	117.862 (117.784)	0.094	0.092
Ethanol	12.79	0.06458	124.659 (124.946)	0.073	0.080
Acetic acid	12.94	0.05306	127.210 (126.780)	0.117	0.105
Methanol	14.50	0.06778	146.654 (146.689)	0.044	0.044

[a] Quantity in parentheses is the value of W back-calculated using Eq. 3.