Dissolution Specifications Based on Release Rates

ZEEV ELKOSHI*

Contribution from *Teva Pharmaceutical Industries Ltd., P.O. Box 353, Kfar-Sava 44102, Israel.*

Received August 6, 1998. Accepted for publication January 4, 1999.

Abstract □ A procedure based on release rates is proposed for the establishment of dissolution specifications that ensure the bioequivalence of a test and a reference product. This procedure, which confines C_{max} (the maximum concentration of the drug in vivo) and AUC_∞ (the area under the time–concentration curve, extrapolated to infinity) values within any desired range (relative to a reference product), can be used as an alternative to the methods presented in the FDA guidance[1] or the USP.[2] The method is appropriate for zero-order or first-order release products with linear Level A in vitro/in vivo correlations (IVIVC). Based on the result that the relative difference in C_{max} must always be smaller than the relative difference in the absorption rate constants (for any test and reference products of a given drug), the "minimum range" specifications are set. These specifications, which are identical for both zero-order and first-order release products, are of general validity. They depend only on the relative extents of release, but are otherwise drug or formulation independent. For certain extended release products demonstrating a constant release rate that is unaffected by dissolution conditions (thus allowing the assumption of Level A IVIVC), the "minimum range" dissolution limits are applicable even when in vivo data is not available. If the reference product in vivo data is available, wider limits (which are product specific) may be set. If the drug disposition is monoexponential, the specifications generated are the widest possible. They are termed the "ideal" specifications. In the case of a multiexponential disposition, the limits set by the procedure will (generally) not be the widest possible. Although the method is based on one-compartment models, it is essentially model independent in the sense that microscopic modeling is redundant for its application.

Introduction

In the presence of in vitro/in vivo correlations (IVIVC), dissolution specifications are important as a means of controlling drug bioavailability and thus can be used as a substitute for human bioequivalence studies. A recently published FDA guidance deals with the application of IVIVC for the setting of dissolution specifications for extended release (ER) products.[1] This guidance includes a section concerning specifications based on the release rate of the product. The section, however, is very brief and refers only to products presenting a zero-order release rate. No method for the establishment of the specifications is included.

The present work proposes a procedure for the determination of rate specifications that ensures the bioequivalence of a tested product and a reference product. This procedure presents an alternative approach to the methods proposed by the USP[2] and FDA guidance.[1] The procedure assumes zero- or first-order release rates and linear Level A IVIVC. Generally, IVIVC are established with in vivo data. Under certain conditions, however, when the rate and extent of release of an ER product are unaffected by dissolution conditions (such as, pH, stirring rate, etc.), linear Level A IVIVC are anticipated (assuming that drug release is the rate-limiting step in the process of in vivo drug absorption).[3] In these cases the procedure is applicable, even in the absence of in vivo data. If the reference product in vivo data are available, the dissolution specifications can be widened.

Although this method is based on monoexponential disposition models, it is also applicable when a multiexponential disposition is involved. The method is essentially model independent in the sense that microscopic modeling is not needed.

The bioequivalence metrics required today by most regulatory agencies are AUC_∞ (the area under the time−concentration curve, extrapolated to infinity) and C_{max} (the maximum concentration of drug in vivo). The specifications produced by the proposed procedure may bound both metrics of a tested product, within any desired range, relative to a reference product, thus ensuring their bioequivalence. In this text, a range of ±20% for both metrics is used.

Setting Dissolution Specifications

Dissolution limits are used as a batch-to-batch quality control means. If in vitro dissolution data are related to in vivo data, these in vitro limits can then be used to control the bioavailability of a tested product, relative to that of a reference product (with a known bioavailability). In this way, the bioequivalence of the two products can be guaranteed in vitro.

Bioavailability and bioequivalence are usually assessed in terms of the C_{max} and AUC_∞ metrics. Most regulatory agencies consider two drugs as bioequivalent when they differ by no more than ±20% with respect to each of these metrics. Hence, dissolution limits that control a ±20% difference between the test metrics and the reference metrics will ensure the bioequivalence of the products. Under these circumstances, quality control is meaningful in terms of the in vivo performance of the drug. Dissolution limits that are set in this way may also be used for a selection of a generic substitute or for the approval of manufacturing changes (drug formulation, drug substance, manufacturing site, etc.).

Dissolution limits that are too wide may allow the approval of batches that are bioinequivalent to a reference product. Limits that are too tight, on the other hand, may lead to the rejection of a large number of production batches. It is desired, therefore, to use the widest possible dissolution specifications that are also consistent with the allowed differences between the test and reference metrics of bioequivalence.

Two sets of dissolution specifications are presented: the "minimum range" and the "ideal" specifications. These two sets are first investigated under the constraint of equal extents of release (between the test and reference products).

* Author to whom all correspondence should be addressed. Telephone: 972-9-7648260. Fax: 972-9-7648636. E-mail address: zeev-e@teva.co.il.

10.1021/js980322p CCC: $18.00
Published on Web 03/13/1999

Then, dissolution specifications for test and reference drugs with different extents of release are considered.

It is assumed throughout this text that linear level A IVIVC are present.

The "Minimum Range" Specifications—The "minimum range" specifications are the widest (relative) dissolution limits that are common to all reference products with IVIVC. Being common to all reference products, the "minimum range" limits must be tighter than the widest feasible dissolution limits for any individual product. Hence, the origin of the name.

It is useful to introduce, at this point, two dimensionless variables, x and y.

For a one-compartment model with zero-order absorption (Appendix A):

$$x = k_{el}D/k_o = k_{el}T \quad (1)$$

where D is the dose absorbed, k_o is the zero-order absorption rate constant, k_{el} is a first-order elimination constant, and T is the duration of the absorption process. Then

$$C_{max} = \frac{D}{Vx}(1 - e^{-x}) \quad (2)$$

where V is the compartment volume.

For a one-compartment model with a first-order absorption (Appendix B):

$$y = k_{el}/k_a \quad (3)$$

where k_a is a first-order absorption constant. Then, by eq B6:

$$C_{max} = \frac{D}{V}y^{y/(1-y)} \quad (4)$$

It is proved in Appendixes A and B that the sensitivity of C_{max} to changes in the rate constant value grows as x or y increase. This result was previously noticed numerically, for the first-order case.[5] The sensitivity reaches a maximum value as $\{x \text{ or } y\} \rightarrow \infty$, where a change in k_o or k_a leads to a change in C_{max} of exactly the same relative value. This, in turn, leads to the conclusion that the in vivo limits $\{\Delta k_o/k_{o(r)} \text{ or } \Delta k_a/k_{a(r)}\} = \pm 0.2$ ensure the condition $|\Delta C_{max}|/C_{max(r)} < 0.2$, where Δ is the test to reference difference and the subscript "r" stands for a reference product. This conclusion is based on the assumption that the test and the reference products are absorbed to the same extent.

If linear level A IVIVC are present, the in vivo absorption rate constants must be linearly related to the in vitro dissolution rate constants. Similarly the (in vivo) extent of absorption must be linearly related to the in vitro extent of release. Therefore, the in vitro condition:

$$-0.2 < \frac{\Delta k_{do}}{k_{do(r)}} \text{ or } \frac{\Delta k_{da}}{k_{da(r)}} < +0.2 \quad (5)$$

where k_{do} or k_{da} are the zero- or first-order dissolution rate constants, respectively, will generally confine the C_{max} value of the test product within ±20% of the reference product value. As before, the Δ sign stands for the test-to-reference difference.

Equation 5 presents the "minimum range" rate specifications when the test and reference products are released to the same extent. The "minimum range" specifications are of general validity because they are not product specific. They are valid even when the drug disposition is multiexponential, as demonstrated in Appendixes C and D. The "minimum range" specifications may be applied for any drug product with established IVIVC. They are particularly useful for certain ER products, where drug release is slow enough and well controlled (see the Discussion). With these products, IVIVC are *expected*. Hence, in these particular cases (and in these cases only), the "minimum range" specifications may be used even when in vivo data are not available.

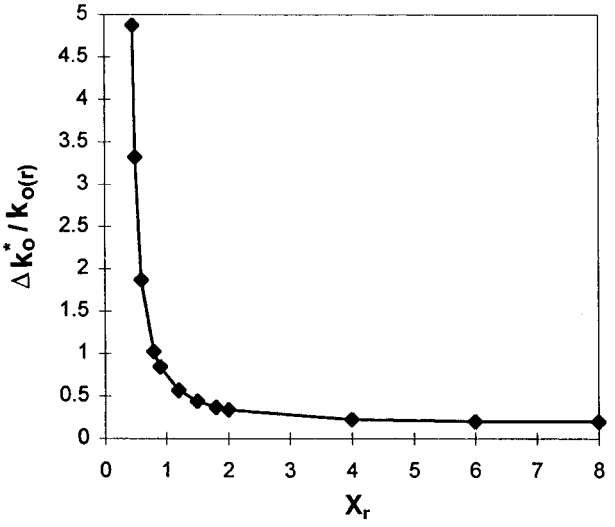

Figure 1—The relative difference in the (zero-order) absorption rate constant values correlating to a standard +20% difference in the C_{max} values, as a function of x_r. The line presents $\Delta k_o^*/k_{o(r)}$ values estimated by the use of eq A11. In the presence of linear IVIVC, the same line defines the upper limit of the "ideal" specifications.

The "Ideal" Specifications—The "ideal" specifications are the widest possible specific dissolution limits that ensure the bioequivalence of any test drug relative to a specific reference product. Similar to the "minimum range" specifications, the "ideal" specification may be applied for any drug product with established IVIVC. However, the "ideal" specifications are dependent on x_r or y_r, which renders the "ideal" specifications product specific.

The widest specific limits of the in vivo absorption rate constants are set in Appendix A (eqs A11 and A12) and Appendix B (eqs B14 and B15) by a test-fitting procedure, assuming one-compartment models with zero- or first-order absorption, respectively. The test and reference products are assumed to be absorbed to the same extent. If linear level A IVIVC are present, the in vivo absorption rate constant (k_o or k_a) is linearly related to the in vitro dissolution rate constant (k_{do} or k_{da}). Similarly, the extent of in vivo absorption is linearly related to the extent of in vitro release.

Hence, when absorption is *zero-order*, the "ideal" dissolution limits are as follows:

Upper limit ($\Delta C_{max}/C_{max(r)} = + 0.2$):

$$\Delta k_{do}^*/k_{do(r)} = 0.0018722x_r^{-9.097} + 0.52492x_r^{-2.003} + 0.2 \quad (6)$$

Lower limit ($\Delta C_{max}/C_{max(r)} = - 0.2$):

$$\Delta k_{do}^*/k_{do(r)} = -0.35753e^{-4.4507x_r} - 0.44063e^{-1.0255x_r} - 0.2 \quad (7)$$

These limits are presented by the lines in Figures 1 and 2.

When absorption is *first-order*, the "ideal" dissolution limits are as follows:

Upper limit ($\Delta C_{max}/C_{max} = + 0.2$):

$$\Delta k_{da}^*/k_{da(r)} = 0.277y_r^{-0.767} + 0.0271y_r^{-3.005} + 0.2 \quad (8)$$

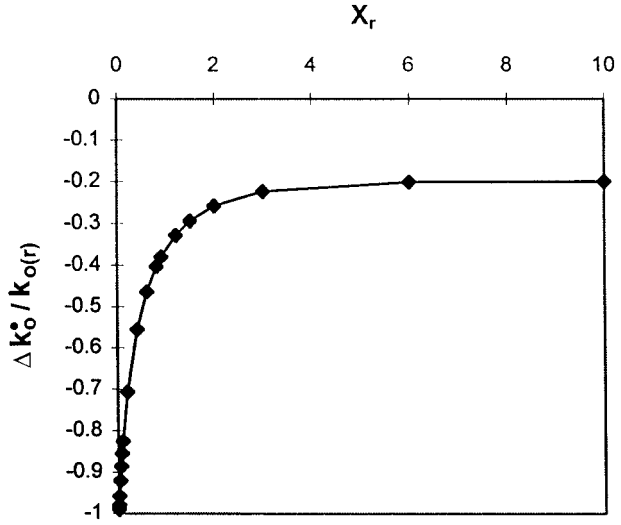

Figure 2—The relative difference in the (zero-order) absorption rate constant values correlating to a standard –20% difference in the C_{max} values, as a function of x_r. The line presents $\Delta k_0^*/k_{o(r)}$ values estimated by the use of eq A12. In the presence of linear IVIVC, the same line defines the lower limit of the "ideal" specifications.

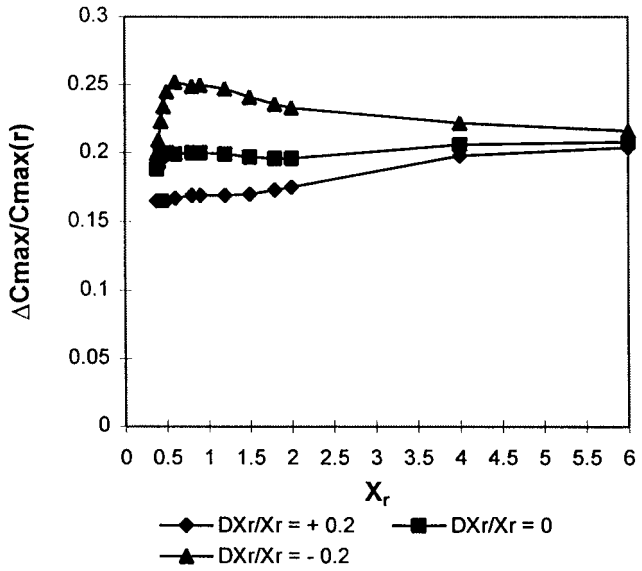

Figure 3—$\Delta C_{max}/C_{max(r)}$ values generated for the zero-order case by using $\Delta k_0^*/k_{o(r)}$ values (defined by eq. A11) in eqs. A5 and A6. The effects of +20% or –20% errors in the estimation of x_r ($Dx_r/x_r = +0.2$ or $Dx_r/x_r = -0.2$) are also included.

Lower limit ($\Delta C_{max}/C_{max(r)} = -0.2$):

$$\Delta k_{da}^{\bullet}/k_{da(r)} = -0.299e^{-26.4y_r} - 0.348e^{-3.128y_r} - 0.146e^{-0.165y_r} - 0.2 \quad (9)$$

These limits are presented by the lines in Figures 3 and 4. Again, Δ is the test-to-reference difference. The (*) and (•) superscripts are reminders that +20% and −20% differences in C_{max}, respectively, are involved.

The use of eqs 6−9 ensures a difference of exactly +20% or −20% between the C_{max} values of the test and reference products. Thus, the range of the rate specifications is the widest possible for each reference product, which renders the "ideal" specifications product specific.

Equations 6 and 8 diverge for $x_r < 0.38$ and $y_r < 0.07$ respectively, indicating that an increase of >20% in C_{max} is *impossible* for x or y values low enough to satisfy these conditions. This leads to the conclusion that a rate-related dose-dumping is impossible when $x < 0.38$ in the zero-order case, or $y < 0.07$ in the first-order case (see Appendixes A and B).

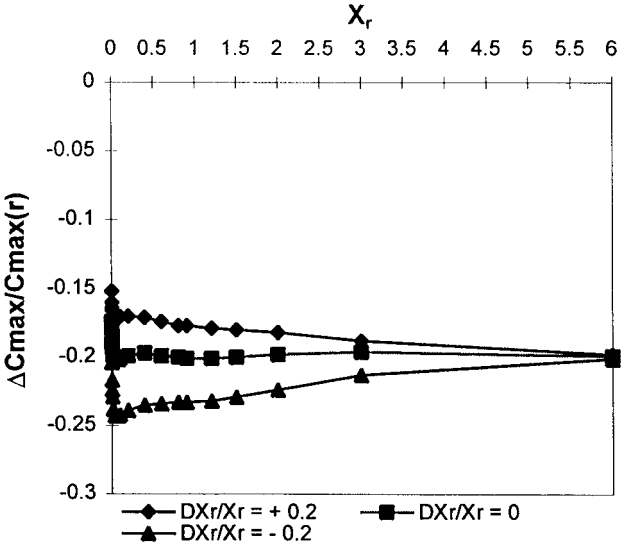

Figure 4—$\Delta C_{max}/C_{max(r)}$ values generated for the zero-order case by using $\Delta k_0^*/k_{o(r)}$ values (defined by eq A12) in eqs. A5 and A6. The effects of +20% or –20% errors in the estimation of x_r ($Dx_r/x_r = +0.2$ or $Dx_r/x_r = -0.2$) are also included.

Like the "minimum range" specifications, the "ideal" specifications are particularly useful for ER products with a well-controlled drug release. In these cases, the "ideal" limits may be applied when the reference product in vivo data are the only in vivo data available (see the Discussion).

Equations 6−9 are useful, even when the disposition of the drug is multiexponential. In this case (as described in Appendixes C and D), k_e in x_r or y_r should be replaced by α_1, the largest macroscopic disposition rate constant. The specifications defined this way are, in general, tighter than the "ideal" specifications (which are not feasible when disposition is multiexponential) and wider than the "minimum range" specifications.

Dissolution Specifications when Products are Absorbed to a Different Extent. It has been postulated so far that both the test and the reference products are released (and hence absorbed) to the same extent. The equations used for the dissolution specifications may be generalized to include the effect of a difference in the extent of release (Appendix E). The "minimum range" specifications in this case are

$$\left.\begin{aligned} -0.2 < \frac{\Delta A}{A_r} < 0.2 \\ -0.2 - \frac{\Delta A}{A_r} < \frac{\Delta k_{do}}{k_{do(r)}} \text{ or } \frac{\Delta k_{da}}{k_{da(r)}} < 0.2 - \frac{\Delta A}{A_r} \end{aligned}\right\} \quad (10)$$

where A is the extent of in vitro release and Δ is the test-to-reference difference.

The "ideal" specifications are generalized by the use of eqs E6 and E7. One of the following two equations should be solved (numerically) to estimate Q, depending on whether the absorption is zero- or first-order:

When absorption is zero-order

$$\frac{1 - e^{-Qx_r}}{Q(1 - e^{-x_r})} - 1 + \frac{\Delta A}{A_r} = \pm 0.2 \quad (11)$$

When absorption is first-order

$$\frac{Qy_r^{Qy_r/(1-Qy_r)}}{y_r^{y_r/(1-y_r)}} - 1 + \frac{\Delta A}{A_r} = \pm 0.2 \qquad (12)$$

where the (+) sign is related to the upper dissolution limit and the (−) sign to the lower dissolution limit.

The "ideal" dissolution limits are then defined by

$$\{\Delta k_{do}/k_{do(r)} \text{ or } \Delta k_{da}/k_{da(r)}\} = 1/Q - 1 \qquad (13)$$

If multiexponential disposition is involved, k_{el} in x_r or y_r (eq 11 or 12) should be replaced by α_1, the largest macroscopic disposition rate constant. In that case, as before, the generated limits are, in general, tighter than the "ideal" limits (which are not feasible, when disposition is multiexponential) and wider than the "minimum range" limits.

Discussion

The conclusion that a 20% change in the value of the in vivo rate constant cannot lead to more than a 20% change in the value of C_{max} is a fundamental result of this work. In the presence of linear IVIVC, this result enables the setting of in vitro "minimum range" dissolution limits that are unspecific to the product and hence are of a general validity. If in vivo data related to the reference product are available, x_r or y_r can be estimated, and the dissolution limits may be widened (by the use of eqs 6−9). The dissolution limits in this case are product specific. The generated limits widen as the x_r or y_r values decrease.

The determination of the in vitro/in vivo correlation coefficients is not required for any of the proposed sets of specifications but in vivo data are generally needed to verify IVIVC. However, when IVIVC are *expected*, the "minimum range" specifications may be set even in the absence of in vivo data. Similarly, when IVIVC are expected, the "ideal" specifications may be set even when only the reference product in vivo data are available. IVIVC are highly probable when the drug release is sufficiently slow and well controlled (i.e., when it is unaffected by dissolution conditions such as pH, stirring rate, ionic strength, surfactant concentration, etc.) Roxatidine controlled/modified-release capsules[3] and the nifedipine push−pull osmotic pump[6,7] are examples. Thus, the proposed specifications, which are valid for any drug product with established IVIVC, are particularly useful when IVIVC are expected. This is not true for methods of setting release specifications based on convolution/deconvolution or modeling techniques where the particular in vitro/in vivo correlation coefficients are required.

It should be emphasized that the availability of in vivo data is always desired, even when linear IVIVC are expected. If in vivo data are available, the validity of the linear IVIVC assumption may be assessed. In addition, wider dissolution limits can be set because x_r or y_r may be evaluated.

Once linear IVIVC have been established (or assumed), dissolution limits are easily set. The "minimum range" limits may always be set with the help of a simple desk calculator. This simplicity is true also with the "ideal" limits when both the test and the reference products are released to the same extent. However, a best-fit procedure is needed to set the "ideal" specifications when the products are released to a different extent.

An interesting and practical result of this work is the observation that for $x < 0.38$ in the zero-order case, or $y < 0.07$ in the first-order case, a rate-dependent dose-dumping (an increase of >20% in C_{max}) is impossible (Appendixes A and B). In other words, formulations with $x < 0.38$ or $y < 0.07$ are dose-dumping proof.

The methods just described do not deal with any microscopic rate constants. The only values derived from the in vivo data are the largest disposition rate constant and either the first-order absorption rate constant or the duration of the zero-order "infusion". All of these are macroscopic constants that do not require any microscopic modeling. In this respect, the procedure is model independent.

For products with a first-order release, it is extremely important to correctly identify the absorption exponential term. A wrong identification (in a "flip-flop" situation) may lead to an underestimation of $y_1(=\alpha_1/k_a)$. The generated dissolution limits, in this case, will allow deviations of the C_{max} value from the ±20% range.

Only when IVIVC prevail can dissolution data be used as a surrogate for the in vivo performance of the drug. From practical experience, the majority of dissolution profiles can be closely approximated by zero- or first-order rates of release. To demonstrate linear Level A IVIVC, the patterns of in vitro release and in vivo absorption profiles must be similar, which means that mainly zero- or first-order in vivo absorption profiles can linearly be correlated with the in vitro data. The more complex absorption curves originating due to the changing physiological environment along the gastrointestinal tract, (usually) cannot be linearly correlated with the (simple) in vitro release curves. Hence, a procedure for the establishment of dissolution specifications, that deals with zero-or first-order release rates (like the one proposed in this work) covers most cases with linear Level A IVIVC.

References and Notes

1. Guidance for Industry, *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*. CDER, Food and Drug Administration, USA, 1997.
2. *The United States Pharmacopeia (USP 23)*; United States Pharmacopeial Convention: Rockville, MD, 1995; p 1929.
3. Frick, A.; Möller, H.; Wirbitzki, E. Biopharmaceutical characterization of oral controlled/modified-release drug products. In vitro/in vivo correlation of roxatidine. *Eur. J. Pharm. Biopharm*. **1998**, *46*, 313−319.
4. Gibaldi M.; Perrier. D. *Pharmacokinetics*, 2nd ed.; Marcel Dekker: New York and Basel, 1982.
5. Rostami-Hodjegan, A.; Jackson, P. R.; Tucker, G. T. Sensitivity of indirect metrics for assessing "rate" in bioequivalence studies-moving the "goalposts" or changing the "game". *J. Pharm. Sci.* **1994**, *83*, 1554−1556.
6. Grundy, J. S.; Foster, R. T. The nifedipine gastrointestinal therapeutic system (GITS): Evaluation of pharmaceutical, pharmacokinetic and pharmacological properties. *Clin. Pharmacokinet*. **1994**, *30(1)*, 28−51.
7. Swanson, R. D., Barclay, B. L., Wong, P. S., Theeuwes, F. Nifedipine gastrointestinal therapeutic system. *Am. J. Med.* **1987**, *83 (Suppl. 6B)*, 3−9.

Acknowledgments

The author is indebted to Dr. Daniel Teitel for editing the manuscript. The assistance of Mrs. Lea Avivi, Mrs. Sarie Nir, and Mr. Michael Cogan is gratefully acknowledged.

Appendix A: One-Compartment Model with Zero-Order Absorption

Consider a one-compartment open model with a zero-order absorption. Define the dimensionless variable x

$$x = k_{el}\, T \qquad (A1)$$

where T is the duration of the absorption process (the

"infusion" time) and k_{el} is a first-order elimination constant. Then

$$C_{max} = \frac{D}{Vx}(1 - e^{-x}) \quad \text{(A2)}$$

where D is the dose absorbed and V is the compartment volume.[4]

The following question is addressed: How is a (macroscopic) difference between the (zero-order) absorption rate constants of two products related to the difference in their C_{max} values? Equation A1 may be rewritten as

$$x = \frac{k_{el}\, D}{k_o} \quad \text{(A3)}$$

where k_o is the zero-order absorption rate constant. Consider test and reference products with equal D, V, and k_{el} values.

The absorption rate constant of the test product, $k_{o(t)}$, has a different value from that of the reference product, $k_{o(r)}$.

Define

$$Q = \frac{x_t}{x_r} = \frac{k_{o(r)}}{k_{o(t)}} \quad \text{(A4)}$$

Then

$$\frac{\Delta k_o}{k_{o(r)}} = \frac{k_{o(t)} - k_{o(r)}}{k_{o(r)}} = \frac{1}{Q} - 1 \quad \text{(A5)}$$

By eqs A2 and A4

$$\frac{\Delta C_{max}}{C_{max(r)}} = \frac{C_{max(t)} - C_{max(r)}}{C_{max(r)}} = \frac{1 - e^{-Qx_r}}{Q(1 - e^{-x_r})} - 1 \quad \text{(A6)}$$

At the limit, as $x_r \to \infty$

$$\lim_{x_r \to \infty} \frac{\Delta C_{max}}{C_{max(r)}} = \frac{1}{Q} - 1 = \frac{\Delta k_o}{k_{o(r)}} \quad \text{(A7)}$$

Hence, as $x_r \to \infty$, the relative difference in C_{max} is equal to the relative difference in k_o.

Derive x with respect to k_o

$$\frac{dx}{dk_o} = -\frac{k_{el} D}{k_o^{\,2}} = -\frac{x}{k_o} \quad \text{(A8)}$$

The infinitesimal relative difference in C_{max} is defined by

$$\frac{dC_{max}}{C_{max}} = \frac{C'_{max}}{C_{max}} dx = -\frac{C'_{max}\, x}{C_{max}} \frac{dk_o}{k_o} = \left[\frac{1 - e^{-x}(x+1)}{1 - e^{-x}}\right] \frac{dk_o}{k_o} \quad \text{(A9)}$$

where eq A8 was used, and C'_{max} is the derivative of C_{max} with respect to x.

Define

$$F(x) = \frac{1 - e^{-x}(x+1)}{1 - e^{-x}} \quad \text{(A10)}$$

It may be proven (Appendix F) that $F(x)$ is a positive and monotone increasing function of x for $x > 0$.

As $x \to \infty$, $F(x)$ assumes its maximal value and therefore, for a constant value of dC_{max}/C_{max}, dk_o/k_o is minimal (by its absolute value) at that limit.

It is demonstrated in Appendix G that the macroscopic quantity $|\Delta k_o|/k_{o(r)}$ corresponding to a constant value of $|\Delta C_{max(r)}|/C_{max}$, assumes a minimum value as $x_r \to \infty$.

This value, which is equal (by eq A7) to $|\Delta C_{max}|/C_{max(r)}$ is a lower boundary to $|\Delta k_o|/k_{o(r)}$ (at any x_r) that corresponds to a constant relative difference between the C_{max} values. In other words, a relative difference of $\pm q$ in k_o corresponds to a relative difference in C_{max}, which is less than q by its absolute value. When $x_r \to \infty$, this relative difference in C_{max} approaches q (by its absolute value).

Hence, the in vivo limits $\Delta k_o/k_{o(r)} = \pm 0.2$ ensure the condition: $|\Delta C_{max}|/C_{max(r)} < 0.2$. These limits will be termed the "minimum range" limits. The "minimum range" limits are the widest (relative) rate constant limits common to all reference products. Being common to all reference products, the "minimum range" limits must be tighter than the widest feasible rate constant limits for any individual product. Hence the origin of the name.

Using eqs A5 and A6 it is possible to estimate (numerically) the value of $\Delta k_o/k_{o(r)}$ correlating to a certain relative difference in $C_{max,}$ as a function of x_r. Figure 1 depicts the best fitted $\Delta k_o/k_{o(r)}$ values related to $\Delta C_{max}/C_{max(r)}$ value of $+0.2$. An asterisk was added as a reminder that a standard $+20\%$ difference in C_{max} is involved.

For $x_r < 0.38$, $\Delta k_o^*/k_{o(r)}$ values diverge. This result means that an infinite relative increase in the $k_{o(r)}$ value is needed when $x_r < 0.38$ to observe a $+20\%$ change in C_{max}. Therefore, dose-dumping (due to a difference in the drug release rate) is not expected when $x_r < 0.38$. This is a consequence of the fact that for $x_r < 0.38$, C_{max} is closer to its maximal value (at $x \sim 0$) by $<20\%$.

The data presented in Figure 1 fit the equation

$$\Delta k_o^*/k_{o(r)} = 0.0018722 x_r^{-9.097} + 0.52492 x_r^{-2.003} + 0.2 \quad \text{(A11)}$$

The $\Delta k_o^*/k_{o(r)}$ values estimated with eq A11 are presented by the line in Figure 1. The accuracy of eq A11 was tested by using $\Delta k_o^*/k_{o(r)}$ values estimated by eq A11 in eqs A5 and A6 to evaluate $\Delta C_{max}/C_{max(r)}$. With 20 x_r values in the range $\{0.38 < x_r < 100\}$ the relative difference in C_{max} was close to 0.2 (ranging from 0.189 to 0.209), as presented in Figure 3. Figure 2 depicts the best fitted $\Delta k_o/k_{o(r)}$ values related to a $\Delta C_{max}/C_{max(r)}$ value of -0.2. The $(\bullet)$ superscript is a reminder that a standard -20% difference in C_{max} is involved. The data presented in Figure 2 fit the equation

$$\Delta k_o^\bullet/k_{o(r)} = -0.35753 e^{-4.4507 x_r} - 0.44063 e^{-1.0255 x_r} - 0.2 \quad \text{(A12)}$$

The fit is presented by the line in Figure 2. The accuracy of eq A12 was examined by using the values generated by this equation in eqs A5 and A6 to evaluate $\Delta C_{max}/C_{max(r)}$. The relative difference between the C_{max} values was close to -0.2 [from (-0.190) to (-0.202)] for 20 x_r values in the range $\{0.008 < x_r < 100\}$, as presented in Figure 4.

Equations A11 and A12 define the relative differences in the absorption rate constant values that are consistent with exactly $+20\%$ or -20% difference between the C_{max} values. Therefore, these equations constitute *the widest* possible absorption rate constant limits that ensure the bioequivalence of test and reference products. Hence, they will be termed the zero-order absorption "ideal" limits. The "ideal" limits are specific to each reference product.

An error in the estimation of $\Delta k_o^*/k_{o(r)}$ or $\Delta k_o^\bullet/k_{o(r)}$ by eqs A11 or A12 may result from a misevaluation of x_r. This misevaluation will lead to $\Delta C_{max}/C_{max(r)}$ values different from the expected values of $\sim +0.2$ or ~ -0.2, respectively. Figure 3 includes the effects of $+20\%$ or -20% errors in the estimation of x_r on the value of $\Delta C_{max}/C_{max(r)}$, when its

expected value is $\sim +0.2$ (i.e. when eq. A11 is used for an estimation of $\Delta k_o^*/k_{o(r)}$). In a similar way, Figure 4 includes the effect of +20% or −20% errors in the estimation of x_r on the value of $\Delta C_{max}/C_{max(r)}$ when its expected value is ~ -0.2 (i.e., when eq A12 is used for an estimation of $\Delta k_o^\bullet/k_{o(r)}$). An overestimation of x_r will lead to $|\Delta C_{max}|/C_{max(r)} < 0.2$. In this case, the $\Delta k_o^*/k_{o(r)}$ and $\Delta k_o^\bullet/k_{o(r)}$ values estimated with eqs A11 and A12 will lead to $\Delta C_{max}/C_{max(r)}$ values within the assumed boundary. However, when x_r is underestimated, $|\Delta C_{max}|/C_{max(r)} > 0.2$. The effect of an error in the estimation of x_r is especially pronounced for low values of x_r. Therefore, when the precise value of x_r is uncertain, it is good practice to use its highest estimated value to evaluate $\Delta k_o^*/k_{o(r)}$ or $\Delta k_o^\bullet/k_{o(r)}$. The resultant $\Delta C_{max}/C_{max(r)}$ value will then probably be confined within the ± 0.2 limits.

If the x_r value is unknown, using the "minimum range" rate limits: $\Delta k_o/k_{o(r)} = \pm 0.2$ will ensure the condition: $|\Delta C_{max}|/C_{max} < 0.2$.

Generally, it is desired to set the widest limits (on a variable) that are consistent with a certain constraint. The "ideal" limits are always wider than the "minimum range" limits. On the other hand, the "ideal" limits may be used only when the reference in vivo rate constants are known.

Appendix B: One-Compartment Model with First-Order Absorption

Consider a one-compartment open model with first-order absorption. The parameter C_{max} is given by[4]

$$C_{max} = \frac{k_a D}{V(k_a - k_{el})}(e^{-k_{el}t_{max}} - e^{-k_a t_{max}}) \qquad (B1)$$

where k_a is a first-order absorption constant. The parameter t_{max} is given by

$$t_{max} = \frac{1}{k_a - k_{el}}\ln[k_a/k_{el}] \qquad (B2)$$

Define the dimensionless variable y

$$y = k_{el}/k_a \qquad (B3)$$

Then, by eq B2,

$$e^{-k_{el}t_{max}} = y^{y/(1-y)} \qquad (B4)$$

$$e^{-k_a t_{max}} = y^{1/(1-y)} \qquad (B5)$$

Using eqs B4 and B5 in eq B1 produces

$$C_{max} = \frac{D}{V} y^{y/(1-y)} \qquad (B6)$$

It is of interest to investigate the effect of a (macroscopic) difference between the (first-order) absorption rate constants of two products on their relative C_{max} values. Consider test and reference products with equal D, V, and k_{el} values. The first-order rate constant of the test product, $k_{a(t)}$ has a different value from that of the reference product, $k_{a(r)}$.

Define

$$Q = \frac{y_t}{y_r} = \frac{k_{a(r)}}{k_{a(t)}} \qquad (B7)$$

Then

$$\frac{\Delta k_a}{k_{a(r)}} = \frac{k_{a(t)} - k_{a(r)}}{k_{a(r)}} = \frac{1}{Q} - 1 \qquad (B8)$$

Equation B8 is identical to eq A5 except that here first-order constants are involved. By the use of eq B6,

$$\frac{\Delta C_{max}}{C_{max(r)}} = \frac{C_{max(t)} - C_{max(r)}}{C_{max(r)}} = \frac{y_t^{y_t/(1-y_t)} - y_r^{y_r/(1-y_r)}}{y_r^{y_r/(1-y_r)}} = \frac{(Qy_r)^{Qy_r/(1-Qy_r)} - y_r^{y_r/(1-y_r)}}{y_r^{y_r/(1-y_r)}} = \frac{(Qy_r)^{Qy_r/(1-Qy_r)}}{y_r^{y_r/(1-y_r)}} - 1 \qquad (B9)$$

At the limit as $y_r \to \infty$,

$$\lim_{y_r \to \infty} \frac{\Delta C_{max}}{C_{max(r)}} = \frac{1}{Q} - 1 = \frac{\Delta k_a}{k_{a(r)}} \qquad (B10)$$

Equation B10 is identical to eq A7. By eq B10, as $y_r \to \infty$, the relative difference in C_{max} is equal to the relative difference in k_a.

Derive y with respect to k_a

$$\frac{dy}{dk_a} = -\frac{k_{el}}{k_a^2} = -\frac{y}{k_a} \qquad (B11)$$

The infinitesimal relative difference in C_{max} is defined by

$$\frac{dC_{max}}{C_{max}} = \frac{C'_{max}}{C_{max}}dy = -\frac{C'_{max}}{C_{max}} y \frac{dk_a}{k_a} = \left[\frac{(y - 1 - \ln y)y}{(1-y)^2}\right]\frac{dk_a}{k_a} \qquad (B12)$$

where eq B11 was used and C'_{max} is the derivative of C_{max} with respect to y (derivation of eq B6).

Define

$$G(y) = \frac{(y - 1 - \ln y)y}{(1-y)^2} \qquad (B13)$$

It may be proven (see Appendix H) that $G(y)$ is a positive and monotone increasing function of y, for $y > 0$ ($y \neq 1$). Therefore, as $y \to \infty$, $G(y)$ assumes a maximal value. Hence, by eq B12, for a constant value of dC_{max}/C_{max}, dk_a/k_a is minimal (by its absolute value) as $y \to \infty$, exactly as in the zero-order model when $x \to \infty$.

By replacing x with y and k_o with k_a in Appendix G, it is demonstrated that the macroscopic quantity $|\Delta k_a|/k_{a(r)}$, corresponding to a constant value of $|\Delta C_{max}|/C_{max(r)}$ assumes a minimum value as $y_r \to \infty$, just as in the zero-order model when $x_r \to \infty$. This value, which is equal (by eq B10) to $|\Delta C_{max}|/C_{max(r)}$, is a lower boundary of the absolute value of $|\Delta k_a|/k_{a(r)}$ (at any y_r) that corresponds to a constant relative difference in C_{max}. In other words, a relative difference of $\pm q$ in k_a corresponds to a relative difference in C_{max} that is less than q by its absolute value. When $y_r \to \infty$, this relative change in C_{max} approaches q (by its absolute value). Hence the in vivo "minimum range" limits $\Delta k_a/k_{a(r)} = \pm 0.2$, ensure the condition $\Delta C_{max}/C_{max(r)} < 0.2$, just as in the zero-order case.

Using eqs B8 and B9, it is possible to estimate (numerically) the value of $\Delta k_a/k_{a(r)}$ corresponding to a certain relative difference in C_{max} as a function of y_r. Figure 5 depicts the best fitted $\Delta k_a/k_{a(r)}$ values related to a $\Delta C_{max}/C_{max(r)}$ value of ± 0.2. Like before, the asterisk stands for a standard +20% difference in C_{max}. For $y_r < 0.07$, the $\Delta k_a/k_{a(r)}$ values diverge, indicating that under this condition, a

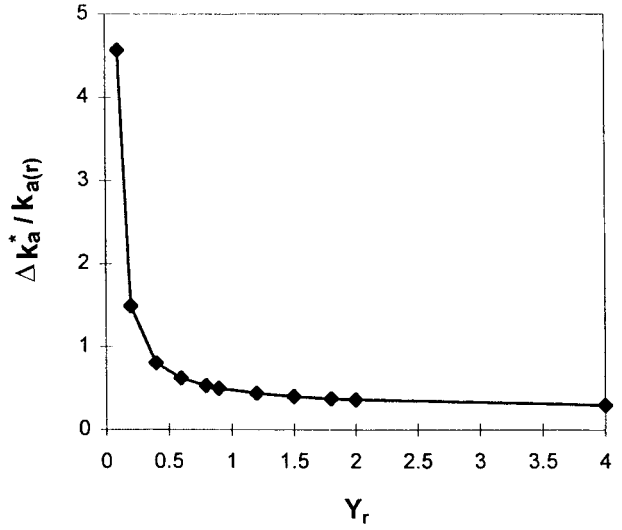

Figure 5—The relative difference in the (first-order) absorption rate constant values correlating to a standard +20% difference in the C_{max} values, as a function of y_r. The line presents $\Delta k_a^*/k_{a(r)}$ values estimated by the use of eq B14. In the presence of linear IVIVC, the same line defines the upper limit of the "ideal" specifications.

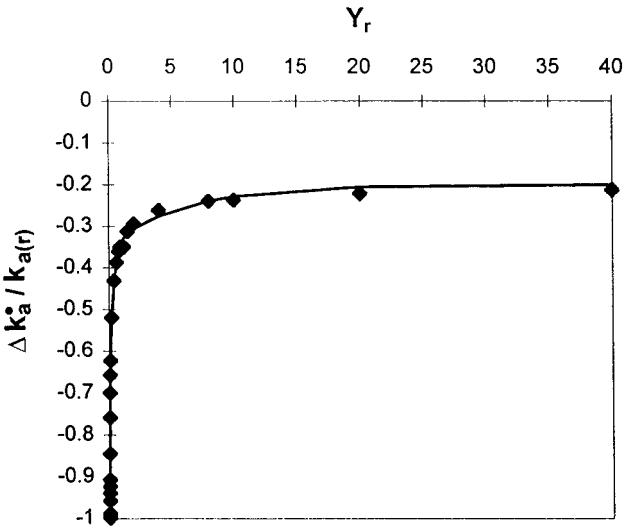

Figure 6—The relative difference in the (first-order) absorption rate constant values correlating to a standard –20% difference in the C_{max} values, as a function of y_r. The line presents $\Delta k_a^\bullet/k_{a(r)}$ values estimated by the use of eq B15. In the presence of linear IVIVC, the same line defines the lower limit of the "ideal" specifications.

+20% difference in C_{max} (a dose-dumping due to a difference in the release rates) is impossible. This is a consequence of the fact that, for $y_r < 0.07$, C_{max} is closer to its maximal value (at $y \sim 0$) by <20%.

The data presented in Figure 5 fit the equation

$$\Delta k_a^*/k_{a(r)} = 0.277 y_r^{-0.767} + 0.0271 y_r^{-3.005} + 0.2 \qquad \text{(B14)}$$

The $\Delta k_a^*/k_{a(r)}$ values estimated with eq B14 are presented by the line in Figure 5. The accuracy of eq B14 was tested by using the estimated $\Delta k_a^*/k_{a(r)}$ values in eqs B8 and B9 to evaluate $\Delta C_{max}/C_{max(r)}$. Twenty y_r values in the range $\{0.07 < y_r < 100\}$ were examined. The relative difference in C_{max} was close to 0.2 (from 0.184 to 0.201), as presented in Figure 7.

Figure 6 depicts the best fitted $\Delta k_a/k_{a(r)}$ value related to a $\Delta C_{max}/C_{max(r)}$ value of −0.2. The (•) superscript, as in the zero-order model, stands for a standard −20% difference

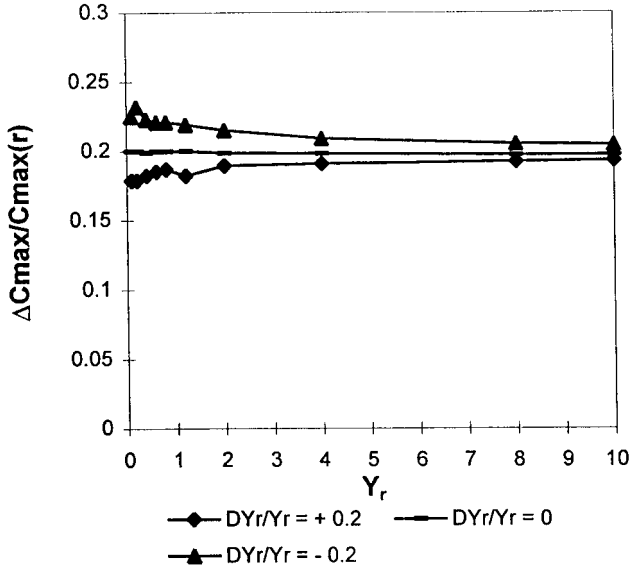

Figure 7—$\Delta C_{max}/C_{max(r)}$ values generated for the first-order case by using $\Delta k_a^*/k_{a(r)}$ values (defined by eq B14) in eqs. B8 and B9. The effects of +20% or −20% errors in the estimation of y_r ($Dy_r/y_r = +0.2$ or $Dy_r/y_r = -0.2$) are also included.

in C_{max}. The data presented in Figure 6 fit the equation

$$\Delta k_a^\bullet/k_{a(r)} = -0.299\, e^{-26.4 y_r} - 0.348\, e^{-3.128 y_r} - 0.146\, e^{-0.165 y_r} - 0.2 \qquad \text{(B15)}$$

The fit is presented by the line in Figure 6. The accuracy of eq B15 was examined, like before, by using the values generated by this equation in eqs B8 and B9 to evaluate $\Delta C_{max}/C_{max(r)}$. With 20 y_r values examined in the range $\{0.004 < y_r < 100\}$, the $\Delta C_{max}/C_{max(r)}$ values were between −0.186 and −0.212, as presented in Figure 8.

Like eqs A11 and A12, eqs B14 and B15 define the relative differences in the absorption rate constant values, consistent with exactly +20% or −20% differences between the C_{max} values. Therefore, these equations provide *the widest* possible rate constant limits that ensure the bioequivalence of the test and reference products. They will be termed the first-order absorption "ideal" limits. These limits are specific to each reference product.

An error in the estimation of $\Delta k_a^*/k_{a(r)}$ or $\Delta k_a^\bullet/k_{a(r)}$ by eqs B14 or B15 may result from a misevaluation of y_r. This misevaluation will lead to $\Delta C_{max}/C_{max(r)}$ values different from the expected values of $\sim +0.2$ or ~ -0.2, respectively. Figure 7 presents the effects of +20% or −20% errors in the estimation of y_r on the value of $\Delta C_{max}/C_{max(r)}$, when its expected (standard) value is $\sim +0.2$ (i.e., when eq B14 is used for the estimation of $\Delta k_a^*/k_{a(r)}$). In a similar way, Figure 8 presents the effect of +20% or −20% errors in y_r on the value of $\Delta C_{max}/C_{max(r)}$ when its expected (standard) value is ~ -0.2 (i.e., when eq B15 is used for an estimation of $\Delta k_a^\bullet/k_{a(r)}$). As in the zero-order case, an overestimation of y_r will lead to $\Delta C_{max}/C_{max(r)}$ values within the boundaries assumed. However, when y_r is underestimated, $\Delta C_{max}/C_{max(r)} > 0.2$. As before, the effect of an error in y_r is especially pronounced for low y_r values.

When the precise value of y_r is uncertain, it is a good practice to use its highest estimated value in eqs B14 and B15. If the y_r value is unknown, the "minimum range" limits $\Delta k_a/k_{a(r)} = \pm 0.2$ should be used. The "ideal" limits are always wider. They are, however, feasible only when the reference in vivo data are available.

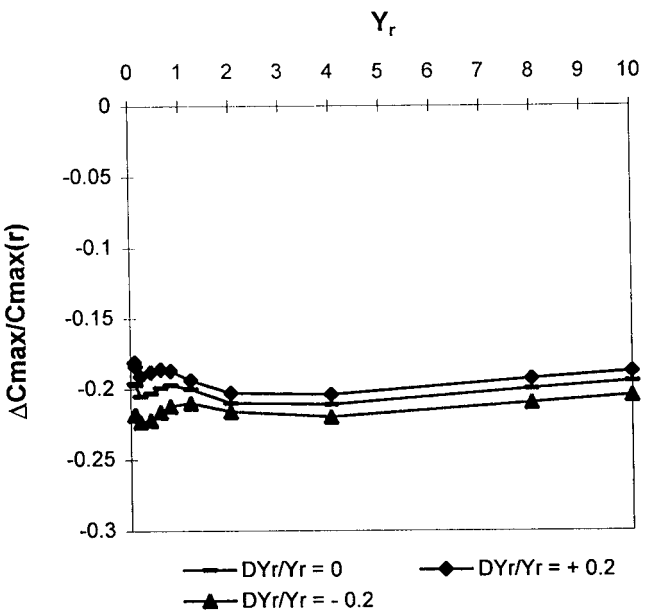

Figure 8—$\Delta C_{max}/C_{max(r)}$ values generated for the first-order case by using $\Delta k_a^*/k_{a(r)}$ values (defined by eq. B15) in eqs B8 and B9. The effects of +20% or –20% errors in the estimation of y_r ($Dy_r/y_r = +0.2$ or $Dy_r/y_r = -0.2$) are also included.

Appendix C: Multicompartment Model with Zero-Order Absorption

When the disposition phase of a drug with a zero-order absorption is appropriately described by n exponential terms, with n first-order rate constants: $\alpha_1 > \alpha_2 > ... > \alpha_n$, the dependence of C_{max} on the zero-order rate constant is specific to the kinetic model involved. Consider an n-compartment model with a zero-order absorption and m (microscopic) first-order disposition rate constants k_j (j = 1, ... m). When elimination occurs from the central compartment, the concentration in this compartment (while absorption is continuing) is given by[4]

$$C(t) = \frac{D/T}{V_c}\sum_{l=1}^{n}\frac{(1-e^{-\alpha_l t})\prod_{i=2}^{n}(E_i-\alpha_l)e^{-\alpha_l t}}{-\alpha_l\prod_{\substack{i=1\\ i\neq l}}^{n}(\alpha_i-\alpha_l)} \qquad (C1)$$

where V_c is the volume of the central compartment and E_i is the sum of the exit rate constants from the i^{th} compartment. The parameter α_l can be expressed in terms of the k_j values (it is not dependent on other physical constants). Because α_l has the same dimensions as k_j (time^{-1}), α_l is a homogeneous function of the first degree with respect to the k_j values. That is, α_l (k_1, ..., k_m) satisfies the identity

$$\alpha_l(qk_1,....qk_m) = q\alpha_l(k_1,....k_m) \qquad (C2)$$

where q is any number.

Equations C1 and C2 imply

$$C(D/V_cT,k_1,....,k_m,t) = C(qD/V_cT,qk_1,...,qk_m,t/q) \qquad (C3)$$

When $t = T$, we have

$$C_{max} = C(D/V_cT,k_1,...k_m,T) = C(qD/V_cT,qk_1,...,qk_m,T/q) \qquad (C4)$$

Using $q = T$ in eq (C4) provides

$$C_{max} = C(D/V_c, k_1T,,...k_mT) \qquad (C5)$$

Therefore, C_{max} is dependent on the m dimensionless variables: k_1T, ... k_mT and on D/V_c. The same conclusion may be reached when the elimination is not from the central compartment or when the concentration involved is that of a peripheral compartment.

The one-compartment model discussed in Appendix A is a special case with $m = 1$ and $k_1 = k_{el}$. As demonstrated

$$C_{max}\text{ (one compartment)} = C(D/V_c, x) \qquad (C6)$$

where $x = k_{el}\ T$.

If a one-compartment model is used (as an approximation) to describe the kinetics of a drug with n exponential disposition terms, the best-fitted disposition rate constant must be smaller than α_1 (and larger than α_n).

Define

$$x_1 = \frac{\alpha_1 D}{k_o}(=\alpha_1 T) \qquad (C7)$$

If $x_{1(r)}$ is used instead of x_r in eq A6, it is reasonable to believe that

$$\frac{|\Delta C_{max}|}{C_{max(r)}} < \frac{1-e^{-Qx_{1(r)}}}{Q(1-e^{x_{1(r)}})} - 1 \qquad (C8)$$

because the $x_{1(r)}$ is an upper boundary of x_r. For the same reason, using $x_{1(r)}$ values as defined by eq C7 in eqs A11 or A12 will generate $|\Delta C_{max}|/C_{max(r)} < 0.2$.

Four different compartment models (with a zero-order absorption) were used to assess this assumption: a classical two-compartment model, a classical three-compartment model, a two-compartment model with a central absorption and a peripheral elimination, and a three-compartment model with a central absorption and a peripheral elimination. Values between 0 and 1 were randomly assigned to the disposition rate constants of each model. For this purpose, a computerized random number generator was used. Ten sets of disposition rate constants were thus produced for each model. For the two-compartment models, the values of the three microscopic disposition rate constants were assigned in this same way. For the three-compartment models, the values of the three macroscopic rate constants and of two of the microscopic rate constants were similarly assigned.

Five absorption rate constant values were defined such that

$$x_{1(r)} = 0.1,\ 0.5,\ 1.5,\ 5,\ 30 \qquad (C9)$$

where eq C7 was used to define $x_{1(r)}$. In this way, a total of 50 different sets of constants were generated for each model.

Equations A11 and A12 with $x_{1(r)}$ substituted for x_r, were utilized to produce $k^*_{o(t)}$ (the upper boundary of $k_{o(t)}$) or $k^\bullet_{o(t)}$ (the lower boundary of $k_{o(t)}$). These values were introduced into the model to estimate $C_{max(t)}$.

In each of the four models examined, the inequality

$$|\Delta C_{max}|/C_{max(r)} < 20\% \qquad (C10)$$

was verified for all 50 data sets. The values for $|\Delta C_{max}|/C_{max(r)}$ were in the range of ~ 1% to 19%. Hence, eqs A11 and A12 (the zero-order "ideal" limits) may be used to assess the absorption rate limits for products with a zero-order absorption and a multiexponential disposition.

The relative rate limits defined by eqs A11 and A12 are wider than ±20% for any finite value of $x_{r(1)}$. Because eq C10 holds when the limits are wider than 20%, it will certainly hold when the relative rate is limited to ±20% (in each of the four models used, for each of the sets of data examined). Thus, the validity of the "minimum range" rate limits is verified for products with a zero-order absorption and a multiexponential disposition.

Appendix D: Multicompartment Model with First-Order Absorption

For the case of multiexponential disposition, consider an *n*-compartment model with a first-order absorption (k_a) and m(microscopic) first-order disposition rate constants k_j ($j = 1,...m$). When the elimination occurs from the central compartment, the concentration in the central compartment is given by[4]

$$C = \frac{k_a D}{V_c} \frac{\prod_{i=2}^{n}(E_i - k_a)}{\prod_{i=1}^{n}(\alpha_i - k_a)} e^{-k_a t} + \frac{k_a D}{V_c} \sum_{l=1}^{n} \frac{\prod_{i=2}^{n}(E_i - \alpha_l)}{(k_a - \alpha_l)\prod_{\substack{i=1 \\ i \neq l}}^{n}(\alpha_i - \alpha_l)} e^{-\alpha_l t} \quad \text{(D1)}$$

where α_l is a first-order macroscopic disposition constant, V_c is the volume of the central compartment, and E_i is the sum of the exit rate constants from the i^{th} compartment.

By eqs C2 and D1, the following identity is satisfied

$$C(D/V_c, k_a, k_1,...,k_m, t) = C(D/V_c, qk_a, qk_1,...,qk_m, t/q) \quad \text{(D2)}$$

where q can be any number.

Therefore, under the transformations

$$k_a \rightarrow qk_a$$

$$k_1 \rightarrow qk_1$$

$$\vdots$$

$$k_m \rightarrow qk_m$$

The value of the untransformed function (at any time point t) is equal to the value of the transformed function (at time point t/q). In particular, the maximum value of the untransformed function (at t_{max}) is equal to the maximum value of the transformed function (at t_{max}/q). Hence

$$C(D/V_c, k_a, k_1,...k_m, t_{max}) = C(D/V_c, qk_a, qk_1,...qk_m, \hat{t}_{max}) \quad \text{(D3)}$$

where $\hat{t}_{max}$ is the time correlating to maximum value of the transformed function.

Therefore, C_{max} is a function of the following variable

$$C_{max} = C(D/V_c, qk_a, qk_1,...,qk_m) \quad \text{(D4)}$$

However, its value is independent of the value of q. The parameter t_{max} is not included among the variables in eq D4 because C_{max} is defined at $t = t_{max}$ (C_{max} is not a function of t_{max}).

Using $q = 1/k_a$ in eq D4 provides

$$C_{max} = C(D/V_c, k_1/k_a,...,k_m/k_a) \quad \text{(D5)}$$

C_{max} is therefore dependent on the m dimensionless variables ($k_1/k_a,...k_m/k_a$) and on D/V_c. The same conclusion may be reached when the elimination is not limited to the central compartment, or when the concentration involved is that of a peripheral compartment.

In the one-compartment case

$$C_{max} = C(D/V_c, k_1/k_a) \quad \text{(D6)}$$

This is demonstrated by eq B6 (with $k_1 = k_{el}$).

Define

$$y_1 = \frac{\alpha_1}{k_a} \quad \text{(D7)}$$

where α_1 is the largest first-order (macroscopic) disposition rate constant. If $y_{1(r)}$ is used instead of y_r in eq B9, it is reasonable to believe that

$$\frac{|\Delta C_{max}|}{C_{max}} < \frac{Qy_{1(r)}^{Qy_{1(r)}/(1-Qy_{1(r)})}}{y_{1(r)}^{y_{1(r)}/(1-y_{1(r)})}} - 1 \quad \text{(D8)}$$

because y_1 is an upper boundary of y. For the same reason, using $y_{1(r)}$ values as defined by eq D7 in eqs B14 or B15 will generate $|\Delta C_{max}|/C_{max} < 0.2$.

For assessing this assumption, the four compartment models used in Appendix C, were utilized with a first-order absorption. The procedure of assigning values to the disposition rate constants was identical to that previously used. The five absorption rate constant values were defined such that

$$y_{1(r)} = 0.1,\ 0.5,\ 1.5,\ 5,\ 30 \quad \text{(D9)}$$

where eq D7 was used to define $y_{1(r)}$. Equations B14 and B15 with $y_{1(r)}$ substituted for y_r were used to produce $k^*_{a(t)}$ (the upper boundary of $k_{a(t)}$) or $\Delta k^{\bullet}_{a(t)}$ (the lower boundary of $k_{a(t)}$). These values were introduced into the model to estimate $C_{max(t)}$.

As in the zero-order models, with each of the four models examined, the inequality

$$|\Delta C_{max}|/C_{max} < 20\% \quad \text{(D10)}$$

was verified for all 50 data sets. Hence, eqs B14 and B15 (the first-order "ideal" limits) may be used to evaluate the absorption rate limit for products with a first-order absorption and a multiexponential disposition.

The relative rate limits defined by eqs B14 and B15 are wider than ±20% for any finite value of $y_{1(r)}$. Hence, it is clear that limiting the relative rate to ±20% will also lead to eq D10 in each of the four models used and for each of the data sets examined. Thus, the "minimum range" limits are applicable for products with a first-order absorption and a multiexponential disposition.

Appendix E: The Effect of a Difference in the Extent of Absorption

It has been postulated, so far, that both test and reference products are absorbed to the same extent. Suppose that each product is absorbed to a different extent.

By the zero-order or the first-order models (mono- or multiexponential disposition), C_{max} may be presented as

$$C_{max} = D \cdot E(z) \tag{E1}$$

where D is the dose absorbed and z stands for either x or y, depending on the model used. The function E depends on the particular model.

Therefore

$$dC_{max} = \frac{\partial C_{max}}{\partial D} dD + \frac{\partial C_{max}}{\partial z} dz \tag{E2}$$

Using eq E1 in eq E2, we get

$$\frac{dC_{max}}{C_{max}} = \frac{dD}{D} + \left[\frac{dC_{max}}{C_{max}}\right]_D \tag{E3}$$

By eq E3, the total relative difference in C_{max} is the sum of the relative difference in D and the "partial" relative difference in C_{max} (when D = constant).

Hence, when the test and reference products are absorbed to a different extent, eq A6 for the zero-order case is generalized as

$$\frac{\Delta C_{max}}{C_{max(r)}} = \frac{1 - e^{-Qx_r}}{Q(1 - e^{-x_r})} - 1 + \frac{\Delta D}{D_r} \tag{E4}$$

Similarly, eq B9 for the first-order case is replaced by

$$\frac{\Delta C_{max}}{C_{max(r)}} = \frac{(Qy_r)^{Qy_r/(1-Qy_r)}}{y_r^{y_r/(1-y_r)}} - 1 + \frac{\Delta D}{D_r} \tag{E5}$$

For the zero-order model, at the limit as $x_r \to \infty$

$$\lim_{x_r \to \infty} \frac{\Delta C_{max}}{C_{max(r)}} = \frac{1}{Q} + 1 + \frac{\Delta D}{D_r} = \frac{\Delta k_o}{k_{o(r)}} + \frac{\Delta D}{D_r} \tag{E6}$$

Similarly, for the first-order model when $y_r \to \infty$

$$\lim_{y_r \to \infty} \frac{\Delta C_{max}}{C_{max(r)}} = \frac{1}{Q} + 1 + \frac{\Delta D}{D_r} = \frac{\Delta k_a}{k_{a(r)}} + \frac{\Delta D}{D_r} \tag{E7}$$

Equations E6 and E7 are generalizations of eqs A7 and B10, respectively.

Appendix F: The Function *F*(*x*)

By eq A10

$$F(x) = \frac{1 - e^{-x}(x + 1)}{1 - e^{-x}}$$

Define

$$f(x) = 1 - e^{-x}(x + 1) \tag{F1}$$

Then

$$f'(x) = xe^{-x} > 0 \text{ for } x > 0 \tag{F2}$$

By eq F1

$$f(0) = 0 \tag{F3}$$

Hence, eq F2 implies

$$f(x) > 0 \text{ for } x > 0 \tag{F4}$$

It is also true that

$$1 - e^{-x} > 0 \quad \text{when} \quad x > 0 \tag{F5}$$

Therefore

$$F(x) = \frac{f(x)}{1 - e^{-x}} > 0 \quad \text{when} \quad x > 0 \tag{F6}$$

Derive $F(x)$ with respect to x

$$F'(x) = \frac{e^{-x}(e^{-x} + x - 1)}{(1 - e^{-x})^2} \tag{F7}$$

Define

$$p(x) = e^{-x} + x - 1 \tag{F8}$$

Then

$$p'(x) = 1 - e^{-x} > 0 \quad \text{when} \quad x > 0 \tag{F9}$$

By eq F8, $p(0) = 0$. Therefore eq F9 implies

$$p(x) > 0 \quad \text{when} \quad x > 0 \tag{F10}$$

It is also true that

$$\frac{e^{-x}}{(1 - e^{-x})^2} > 0 \quad \text{for any } x \tag{F11}$$

Therefore

$$F'(x) = \frac{e^{-x}p(x)}{(1 - e^{-x})^2} > 0 \quad \text{when} \quad x > 0$$

Hence $F(x)$ is a positive monotone increasing function of x for $x > 0$.

Appendix G: The Asymptotic Behavior of $\Delta k_o/k_{o(r)}$

$$\int_r^t \frac{dC_{max}}{C_{max}} = \ln \frac{C_{max(t)}}{C_{max(r)}} = \ln\left(\frac{\Delta C_{max}}{C_{max(r)}} + 1\right) \tag{G1}$$

A constant value of the integral on the left-hand side of eq G1 corresponds to a constant value of $\Delta C_{max}/C_{max(r)}$.

It was proven that the infinitesimal quantity dk_o/k_o, corresponding to a constant infinitesimal relative difference in C_{max} (dC_{max}/C_{max}), is minimal (by its absolute value) as $x \to \infty$. Therefore, the integrated form $\int_r^t dk_o/k_o$ corresponding to a constant value of $\int_r^t dC_{max}/C_{max}$ must also assume a minimum value as $x_r \to \infty$.

Because

$$\int_r^t \frac{dk_o}{k_o} = \ln \frac{k_{o(t)}}{k_{o(r)}} \tag{G2}$$

$|\ln(k_{o(t)}/k_{o(r)})|$, corresponding to a constant value of $\Delta C_{max}/C_{max(r)}$, has a minimum value as $x_r \to \infty$.

When $k_{o(t)}/k_{o(r)} > 1$, both $k_{o(t)}/k_{o(r)}$ and $|k_{o(t)}/k_{o(r)} - 1|$ attain a minimum value as $x_r \to \infty$. When $k_{o(t)}/k_{o(r)} < 1$, $k_{o(t)}/k_{o(r)}$ is maximal as $x_r \to \infty$, whereas $|k_{o(t)}/k_{o(r)} - 1|$ is minimal at this limit.

Hence $|k_{o(t)}/k_{o(r)} - 1|$ $(=|\Delta k_o|/k_{o(r)})$ corresponding to a constant value of $|\Delta C_{max}|/C_{max(r)}$, is minimal as $x_r \rightarrow \infty$.

Appendix H: The Function *G(y)*

By eq B13

$$G(y) = \frac{(y - 1 - \ln y)y}{(1 - y)^2}$$

Define

$$g(y) = y - 1 - \ln y \tag{H1}$$

Then

$$g'(y) = \frac{y - 1}{y} \tag{H2}$$

By eq H2

$$g'(y) > 0 \quad \text{for} \quad y > 1 \tag{H3}$$

$$g'(y) < 0 \quad \text{for} \quad 0 < y < 1 \tag{H4}$$

By eq H1 $g(y = 1) = 0$; hence, eq H3 implies

$$g(y) > 0 \quad \text{for} \quad y > 1 \tag{H5}$$

For the same reason, eq H4 implies

$$g(y) > 0 \quad \text{for} \quad 0 < y < 1 \tag{H6}$$

Therefore

$$G(y) = \frac{g(y)}{(1 - y)^2} y > 0 \quad \text{for} \quad y > 0 \tag{H7}$$

Derive $G(y)$ with respect to y

$$G'(y) = \frac{(y - 1 - \ln y)(1 + y) - (1 - y)^2}{(1 - y)^3} \tag{H8}$$

Define

$$h(y) = (y - 1 - \ln y)(1 + y) - (1 - y)^2 \tag{H9}$$

Then

$$h'(y) = 1 - \ln y - y^{-1} \tag{H10}$$

Suppose $h'(y) = 0$, then by eq H10

$$\ln y = \frac{y - 1}{y} \tag{H11}$$

Equation H11 is satisfied when $y = 1$. Therefore, $y = 1$ is a solution for $h'(y) = 0$. We shall prove that $y = 1$ is the only solution for $h'(y) = 0$ $(0 < y < \infty)$:

When $y > 0$, both $\ln y$ and $(y - 1)/y$ are monotone increasing functions of y, as demonstrated by eqs H12 and H13

$$[\ln y]' = \frac{1}{y} \tag{H12}$$

$$\left[\frac{y - 1}{y}\right]' = \frac{1}{y^2} \tag{H13}$$

By eqs H12 and H13

$$[\ln y]' > \left[\frac{y - 1}{y}\right] \quad \text{for} \quad y > 1 \tag{H14}$$

$$[\ln y]' < \left[\frac{y - 1}{y}\right] \quad \text{for} \quad 0 < y < 1 \tag{H15}$$

Therefore, for $y > 1$, $\ln y$ increases (with y) faster than $(y - 1)/y$, and the functions do not cross each other. For $0 < y < 1$, $\ln y$ decreases (when y decreases) slower than $(y - 1)/y$ and again, both functions do not cross. Therefore, $y = 1$ is the only solution for $h'(y) = 0$ $(0 < y < \infty)$.

A second differentiation of $h(y)$ with respect to y, provides

$$h''(y) = \frac{1}{y} + \frac{1}{y^2} \tag{H16}$$

At $y = 1$

$$h''(y = 1) = 0 \tag{H17}$$

Therefore $y = 1$ is an inflection point of $h(y)$. Because $y = 1$ is the only point where eq H11 holds, $h(y)$ is monotone for $0 < y < \infty$. By substituting any positive value $(\neq 1)$ for y in eq H10, it is found that

$$h'(y) < 0 \tag{H18}$$

Therefore, $h(y)$ is a monotone decreasing function of y for $0 < y < \infty$.

By eq H9

$$h(y = 1) = 0 \tag{H19}$$

Hence

$$h(y < 1) > 0 \tag{H20}$$

$$h(y > 1) < 0 \tag{H21}$$

Therefore

$$G'(y) = \frac{h(y)}{(1 - y)^3} > 0 \quad \text{for} \quad 0 < y < \infty \ (y \neq 1)$$

It may be concluded that $G(y)$ is a positive and monotone increasing function of y for $0 < y < \infty$ $(y \neq 1)$ and it is undefined at $y = 1$.

JS980322P