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Biopharmaceutics Aspects of the Regulatory Review of Oral Controlled-Release Drug Products

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On behalf of the Food and Drug Administration, I wish to thank the Graduate Faculty of Rutgers University for providing this forum to discuss the Biopharmaceutics Aspects of the Regulatory Review of Oral Controlled-Release (CR) products. My goal today is to cover the requirements, as far as bioavailability testing, of the Division of Biopharmaceutics of the FDA. These requirements have two aspects, NDA approval, and therapeutic equivalence. I will be covering the differences in these requirements. We'll take a look at the Bioavailability Regulations as they appear in the Code of Federal Regulations, discuss the FDA interpretation of these Regulations and specific criteria used in the review of bioavailability studies that are submitted as part of an NDA. To illustrate these criteria we'll go over 2 example drugs, papaverine and quinidine gluconate.

Oral controlled release drug products have been marketed for at least the last 30 years (Table 1). The Division of

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TABLE 1

ORAL CONTROLLED - RELEASE
DRUG PRODUCTS

1952	"SPANSULE" MARKETED
1970	FDA REVIEW OF BIOAVAILABILITY
1977	BIOAVAILABILITY/BIOEQUIVALENCE REGULATIONS

Biopharmaceutics of the FDA, and earlier the Division of Clinical Reseach has reviewed submissions involving such drug products only over the last 10 years. In addition, the applicable Bioavailability Regulations have only been in effect for 5 years. From this information, we can conclude three points. First, not all marketed oral controlled-release drug products have undergone bioavailability testing either because bioavailability testing was not possible due to lack of analytical methods or, bioavailability testing was not required since the relevant regulations were not in effect at the time of NDA approval. A second conclusion is that the Regulatory Requirements for bioavailability testing of oral CR drug products are at an evolutionary stage since they have only been recently implemented. It is these requirements that I would like to discuss today. A third conclusion we would reach is that CR drug products are here to stay and in fact will become increasingly seen as greater numbers of such products are marketed both as oral dosage forms such as

tablets, capsules and suspensions and the somewhat more exotic dosage forms such as implants, transdermal patches and inserts. Recent approvals include CR forms of indomethacin, disopyramide, diazepam, and nitroglycerin.

My remarks today are primarily targeted at oral CR drug products, both prescription and over-the-counter, but are generally applicable, with some exceptions, to other types of CR products.

An initial question to be answered is "why is there a need for CR drug products?" (Table 2) We're all familiar with the often cited advantages of CR products - less toxicity including both systemic and local GI disturbances, less drug administration, controlled rate and site of release, more uniform blood levels and improved patient compliance. The vast majority of currently marketed CR products primarily relate to the last point, less frequent dosing and better patient compliance and, as such, provide a valuable addition to a drug's usefulness.

However, I think we've still got a way to go before all the theoretical advantages of CR drug products are realized.

CR products also may have disadvantages (Table 3). First, we have some evidence that certain CR beadlet capsules may be

TABLE 2

POTENTIAL ADVANTAGES OF CONTROLLED RELEASE PRODUCTS

1. DECREASED TOXICITY (SYSTEMIC AND LOCAL)
2. BETTER DRUG UTILIZATION
3. CONTROLLED RATE AND SITE OF RELEASE
4. MORE UNIFORM BLOOD CONCENTRATIONS
5. IMPROVED PATIENT COMPLIANCE (LESS FREQUENT DOSING)

Table 3

POTENTIAL DISADVANTAGES OF CONTROLLED RELEASE PRODUCTS

1. INCREASED VARIABILITY AMONG DOSAGE UNITS
2. STABILITY CONCERNS
3. TOXICITY
4. INCREASED COST
5. MORE RAPID DEVELOPMENT OF TOLERANCE
6. NEED FOR ADDITIONAL PATIENT EDUCATON

subject to extreme content variability problems. Also, dosage-unit to dosage-unit release patterns may be more variable than corresponding immediate release products. Second, the complexity of CR formulations may lead to stability problems resulting in either faster or slower release than anticipated. Third, toxicity may result if the product dose dumps or is misused. We have evidence of

patients crushing non-disintegrating matrix-type CR tablets when the apparently drug-free tablet remains appeared in the stools. Fourth, CR products are generally more expensive than their immediate release counterparts. Fifth, the uniform blood concentrations of CR products may result in more rapid development of tolerance. Finally, patients may need substantially additional information as to the proper use of CR products eg "Don't crush or chew the dosage unit. Tablet remains may appear in the stools." Patients in some instances must be first started on an immediate release product then switched to the CR product.

With this background information in mind, I would like to proceed to the current Division of Biopharmaceutics requirements for oral CR drug products (Table 4).

Since most current oral CR products and NDA submissions for such products involve drug products which are administered less frequently (usually 1/2 as frequently) than an already-approved immediate-release counterpart, the Regulatory Requirements for Bioavailability Testing are somewhat standardized and I'd like to discuss these now.

The F.D.A bioavailability regulations call for firms to provide the following information for their controlled release product.

TABLE 4

REQUIREMENTS OF FDA

BIOAVAILABILITY REGULATIONS

1. THE DRUG PRODUCT MEETS THE CONTROLLED RELEASE CLAIMS MADE FOR IT.
2. THE BIOAVAILABILITY PROFILE ESTABLISHED FOR THE DRUG PRODUCT RULES OUT THE OCCURRENCE IF DOSE DUMPING.
3. THE DRUG PRODUCT'S STEADY - STATE PERFORMANCE IS EQUIVALENT TO CURRENTLY MARKETED, NON-CONTROLLED RELEASE OR CONTROLLED RELEASE DRUG PRODUCT SUBJECT TO AN APPROVED FULL NDA.
4. THE DRUG PRODUCT'S FORMULATION PROVIDES CONSISTENT PHARMACOKINETIC PERFORMANCE BETWEEN INDIVIDUAL DOSAGE UNITS.

(i) The drug product meets the controlled release claims made for it.

(ii) The bioavailability profile established for the drug product rules out the occurrence of dose dumping.

iii) The drug product's steady-state performance is equivalent to currently marketed, noncontrolled release or controlled release drug product subject to an approved full NDA.

(iv) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

TABLE 5

REFERENCE MATERIAL

1. SOLUTION OR SUSPENSION
2. NON-CONTROLLED RELEASE APPROVED PRODUCT
3. CONTROLLED RELEASE APPROVED PRODUCT

The reference material (Table 5) for such studies should usually be:

(i) either a solution or suspension of the active drug ingredient or therapeutic moiety,

(ii) a currently marketed approved noncontrolled release drug product containing the same active drug ingredient or therapeutic moiety, or

(iii) a currently marketed approved controlled release drug product subject to an approved full new drug application containing the same active drug ingredient or therapeutic moiety.

It is the position of the FDA that these requirements are applicable to essentially all CR prescription and over-the-counter drug products including CR products containing pre-1938 active ingredients (these are generally

considered, by the FDA, to be new drugs requiring NDA approval), DESI drugs, and post-1962 drugs.

The biological performance of a CR formulation is defined in terms of the rate at which a dosage form releases active drug and the bioavailability of the dosage form relative to an appropriate standard. The purpose of this requirement is not necessarily to prove that the controlled drug release dosage form is equivalent to a standard dosage form, but rather to establish the bioavailability and controlled nature of the drug release dosage form relative to an appropriate standard in accordance to guidelines published in the January 7, 1977, FEDERAL REGISTER.

Illustrated in Table 6 are some criteria of performance that should be a prerequisite for all controlled release dosage forms.

To demonstrate the performance of a controlled release formulation or drug delivery system, the firm needs to submit both in vitro and in vivo data:

A) In vitro drug release data

These data should be drug release rate profiles generated in a well-designed reproducible in vitro testing method,

Table 6

Criteria of Performance of Controlled Release Dosage Forms

Demonstration of the Controlled Release Nature

1. In vitro data (e.g., Dissolution Rate, Diffusibility)
2. In vivo bioavailability data
   a. Pharmacokinetic data
   b. Bioavailability Comparable to the Reference Dosage Form with Same Labeling in Indications and Side Effects
   c. Bioavailability Nonequivalent to the Reference Dosage Form but Demonstration of Safety and Efficacy and Different Labeling
   d. Reproducibility of In Vivo Performance

such as the dissolution test for solid dosage forms. It should be sensitive enough for discriminating any change in formulation parameters and lot-to-lot variations. The key elements are:

a) Reproducibility of the method
b) Proper choice of medium
c) Maintenance of perfect sink conditions
d) Control of solution hydrodynamics

The manufacturers of controlled release drug products are urged to develop reproducible and sensitive in vitro methods

to characterize the release mechanisms of the controlled release drug products they have developed and intend to market. Ideally, the in vitro test developed can be utilized to characterize the bioavailability of the controlled release dosage forms and can also be relied upon to assure lot-to-lot performance.

B) In vivo bioavailability data

These data consist of:

a) Pharmacokinetic profiles of test and reference products.

b) Bioavailability data - either comparable to the reference dosage form with same labeling in indications and side effects or non-equivalent to the reference dosage form with demonstration of safety and efficacy and different labeling.

c) Evidence of reproducible in vivo performance

The controlled release formulation developed should aim to accomplish two important objectives: (i) It should allow a maximum possible percentage of the dose in the formulation to be absorbed in a controlled manner, and (ii) it should be capable of minimizing patient-to-patient variability. For the

development of a controlled release formulation, one commonly used approach is to modify the rate of release of a drug from the formulation by pharmaceutical manipulation; and, hence potential alteration of the drug absorption rate and plasma levels. Therefore, in so doing, one must assure with scientific evidence that the absorption efficiency of the drug is not appreciably impaired and the variability is not adversely increased. Steady state studies are required in most instances for prescription products. Single dose studies have been accepted for OTC products. However, apparent bioavailability differences observed in a single dose study which may cause the study to be rejected by FDA, may become insignificant at steady-state. For this reason, a steady-state study may be preferable.

More specifically (Table 7), the criteria for evaluation of bioavailability of CR drug products employed by the FDA include some indication that the CR product is not dose-dumping. This may be determined by administering the amount of drug contained in the CR product as an immediate-release oral bolus dose. Rate of absorption of the CR product should be substantially slower, C_{max} should be lower and T_{max} longer, compared to the bolus dose. In a separate study, usually a steady-state study, the bioavailability of CR product compared to an appropriate

TABLE 7

SPECIFIC FDA REVIEW CRITERIA

1. NO DOSE - DUMPING
2. CMAX
3. TMAX
4. AUC
   a) ±20%
   b) 75/75 RULE
5. CONSISTENT PERFORMANCE
   a) SIMILAR VARIABILITY
   b) DISSOLUTION

reference material must be determined. C_{max} for both treatments should be similar particularly if labelling identical to the reference product is anticipated for the CR product. Large difference in C_{max} is unacceptable and may require reformulation or clinical studies to determine the effect of these differences on safety and effectiveness.

T_{max} may very well differ and is generally of little value in the evaluation. Mean AUC of test and reference product should be within 20% of each other. The "75/75 rule "is usually applied to individual AUC values. At least 75% of the subjects tested must have AUC's within the range 75% - 125% compared to the reference product. If the CR product fails

the "75/75 rule," clinical trials may be required to substantiate the safety and efficacy of the product, if such trials have not already been conducted. An example of this would be a highly metabolized drug which has active metabolites. Measuring only parent compound, the CR product may fail the "75/75 rule" yet still be a safe and effective product. Finally, consistent performance of the CR product is evaluated. This is determined by comparing variability of test and reference products and by dissolution data of individual test dosage units. With some exceptions, these are the specific criteria used to evaluate CR drug products.

In the remaining time, I would like to cover two distinct examples to illustrate the application of these criteria, as well as dissolution criteria, to specific drugs.

Papaverine CR products provides an example of a "new drug" product containing an "old drug" ingredient with apparent bioavailability problems.

In a study conducted under FDA contract (Table 8), 9 CR papaverine HCl marketed products were tested in vivo and in vitro. Comparison in vivo was made to oral solution and immediate release tablets. Wide ranges in mean bioavailability were found ranging from 95% for the immediate

TABLE 8

GROUP I

PRODUCT	AUC (0-10 HRS)	% BIOAVAILABILITY
ELIXIR	1307.5	-
LILLY	1247.2	95
MARION	409.2	31
MYLAN	725.2	55
RUCKER	800.0	61
ZENITH	480.7	37

GROUP II

ELIXIR	736.8	-
HEUN/NORWOOD	290.8	39
CENTRAL	183.2	25
KEY	455.3	62
ICN	132.7	18
VITARINE	216.0	29

release tablets to 18 to 62 % for the CR products. The mean bioavailability for Group I are shown in Figure 1. Dissolution testing was conducted on the CR products and similar wide variations were found (Figure 2). The in vivo and in vitro results were found to correlate quite well (Figure 3). These results may at least partially explain the effectiveness questions which surround papaverine. Quinidine gluconate CR tablets provides a good example of (1) the need for bioavailability testing of CR products, (2) the usefulness of dissolution testing of CR products and (3) the criteria for review utilized by the Division of

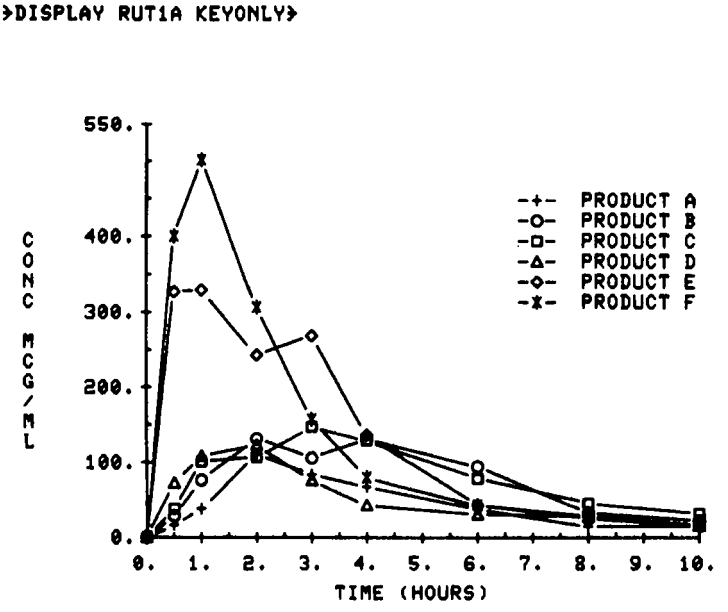

FIGURE 1
Mean plasma concentrations of 6 papaverine hydrochloride products.

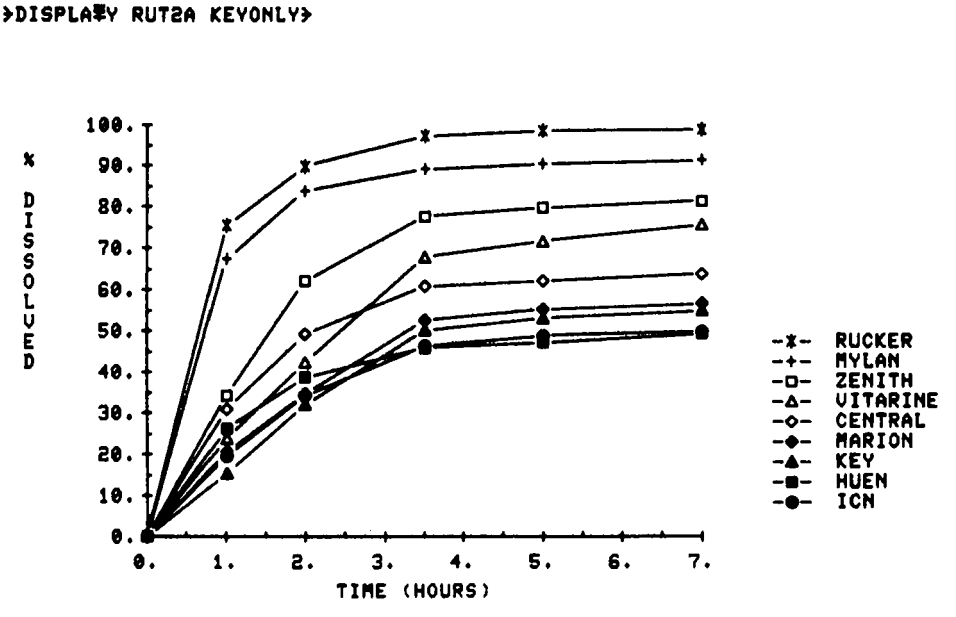

FIGURE 2
Dissolution profile of papaverine hydrochloride controlled-release capsules and tablets.

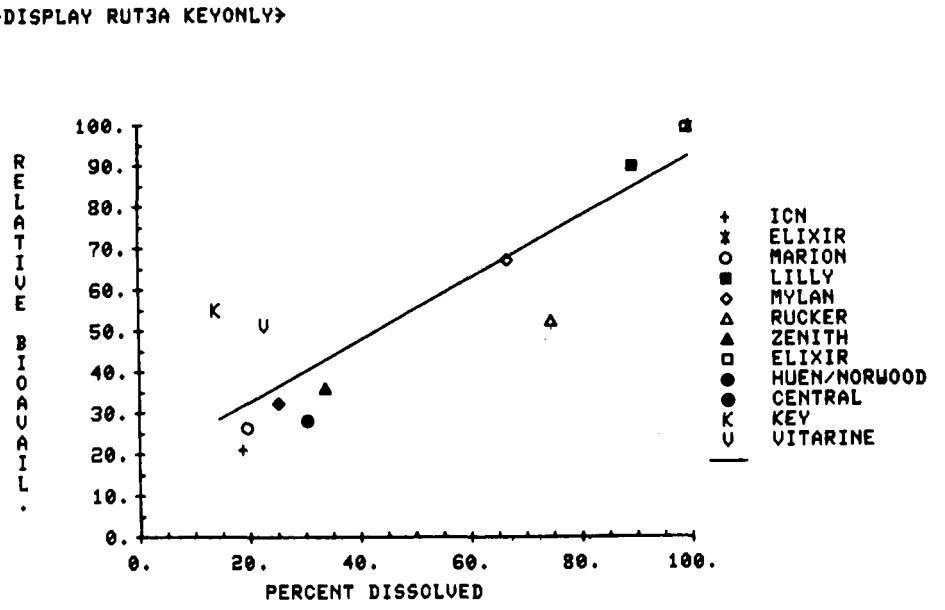

FIGURE 3
In vivo/in vitro correlation for papaverine hydrochloride products.

Biopharmaceutics in evaluating such products. About 2 years ago, the FDA was faced with a number of prescription drug products being marketed without approval of an NDA. Although most of these products involved immediate release dosage forms, at least one, a quinidine gluconate tablet, was a CR product. This product apparently was marketed based on comparable dissolution to the reference product (Quinaglute Dura Tabs - Berlex) in acid medium. Following several reports related to alleged therapeutic failures with the unapproved product and, the submission, by the manufacturer of the reference product, to the FDA, of the results of a bioavailability study showing only 41% bioavailability of the

unapproved product based on AUC, compared to the reference product, the firm recalled this defective product. The firm subsequently reformulated the product, submitted an ANDA and obtained approval. Table 9 summarizes the results of the study comparing the reference product to the product which was recalled. AUC differs greatly, as does C_{max}, showing the usefulness of these parameters. T_{max} differs by only 9%, showing the lack of usefulness of this parameter. Table 10 summarizes the results of a study approved as part of the review of the ANDA for the reformulated test product. Mean AUC's differ by only 2%, C_{max} differs by only 7%. T_{max} differs by 11%, but this 1/2 hour difference would not be expected to be clinically significant. It does indicate that the test product is absorbed somewhat more rapidly than the reference product. Not shown are the individual AUC comparisons. The test product passed the "75/75 rule" under steady-state conditions, whereas single dose results indicated borderline failure of the "75/75 rule". We would consider the steady-state results more meaningful.

We can next look (Figure 4) at the dissolution characteristics of these products. The Biopharmaceutics Laboratory conducted a great deal of dissolution testing on these products. The purpose of this testing was to attempt to develop a correlation between the in vivo data and in vitro dissolution

TABLE 9

In Vivo Data For QUINIDINE GLUCONATE TABLETS

PARAMETER	PRODUCTS BE	BO-1	BO-1/BE X 100
Dose	648 MG	648 MG	
CMAX (MCG/ML)	1.26 ± 0.34	0.47 ± 0.13	35%
TMAX (HR)	3.18 ± 1.20	3.51 ± 0.67	
AUC (MCG/MLXHR)	15.5 ± 4.81	6.38 ± 2.35	41%

Each Value is the Mean ± S.D. of 12 Subjects

TABLE 10

In Vivo Data For Quinidine Gluconate Tablets

Parameter	Products BE	BO-2
Dose	324 MG	324 MG
CMAX (MCG/ML)	0.52 ± 0.22	0.56 ± 0.18
TMAX (HR)	6.1 ± 1.65	5.5 ± 1.27
AUC (MCG/MLXHR)	6.23 ± 2.87	6.37 ± 2.67

Each value is the Mean ± S.D of 20 Subjects

data. Various media were utilized in this attempt. Tested were the reference CR product and the recalled unapproved CR product. Water, pH 5.4 phosphate buffer and pH 5.4 acetate buffer provide for large differences in dissolution for the bioinequivalent products. The pH 5.4 acetate buffer was selected as the final medium since water is unbuffered and pH differences in the dissolution medium were found pre and post-testing. Also, a third product of known, good bioavailability, was found to dissolve well under the pH 5.4 acetate buffer conditions. Figure 5 shows the reformulated product's dissolution.

Subsequent to the approval of the generic manufacturer's product, the innovator company conducted a steady-state study,

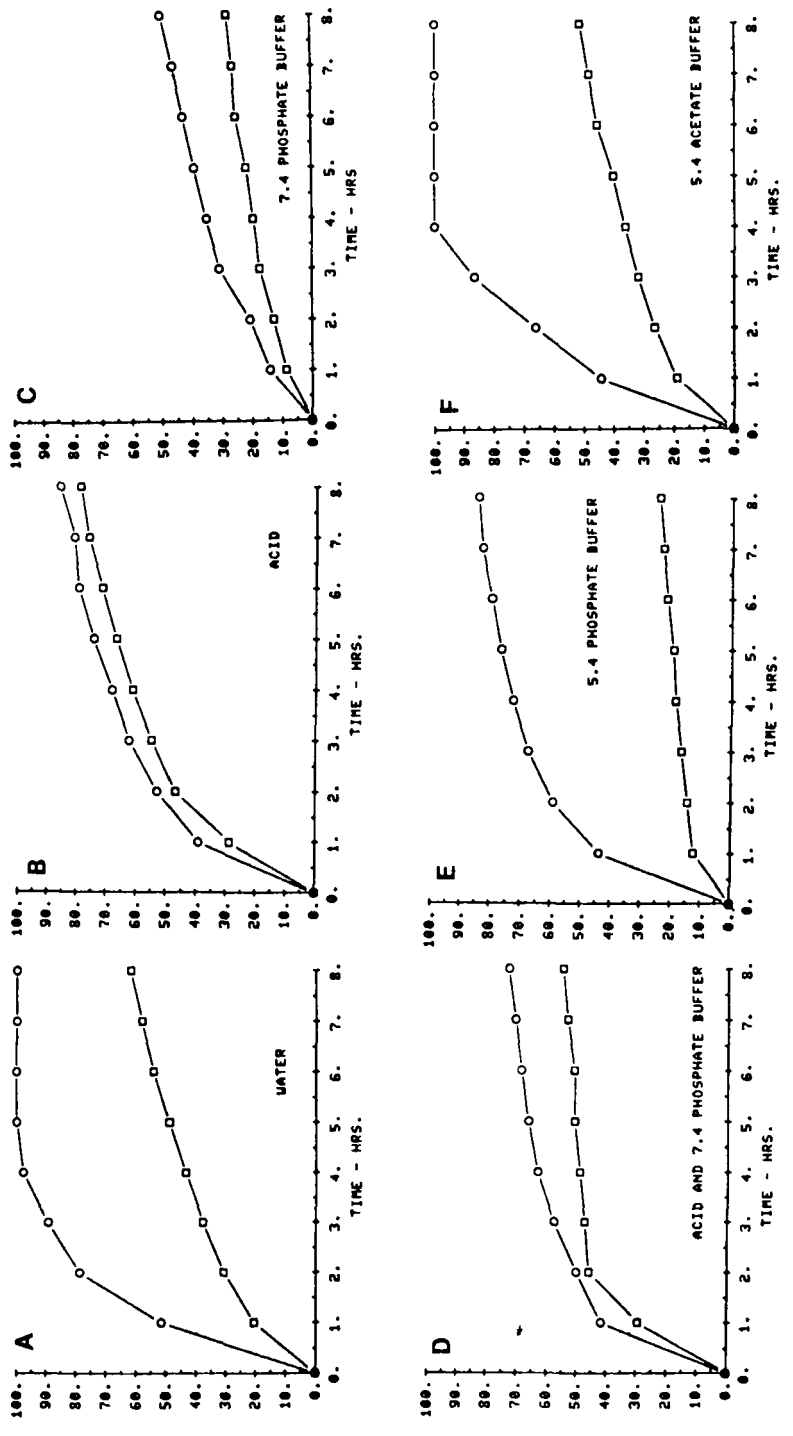

FIGURE 4
Dissolution profile of two quinidine gluconate controlled-release products in different dissolution media.

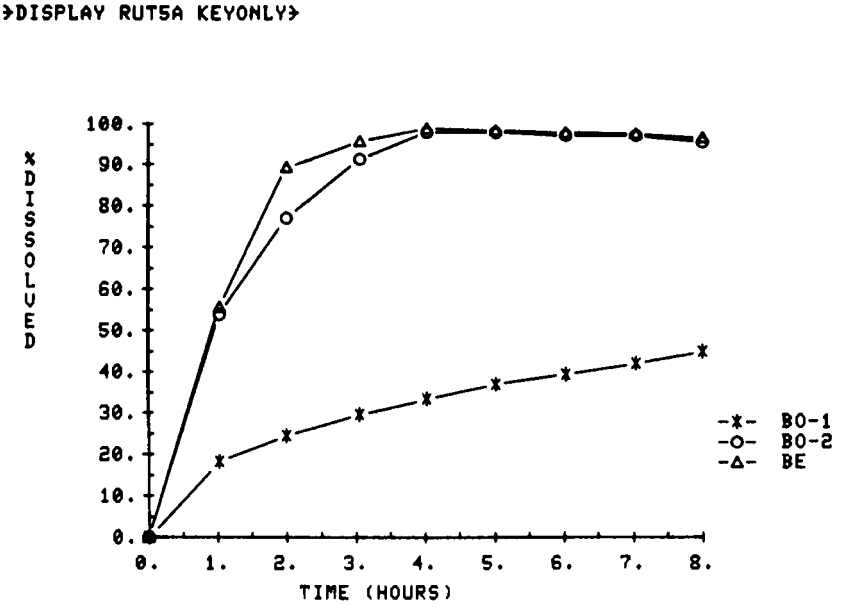

FIGURE 5
Dissolution profile of three quinidine gluconate products in pH 5.4 acetate buffer (paddle at 100 rpm).

submitted the results to the FDA, concluding that the products were not bioequivalent based on 13% differences in mean AUC and significant differences in mean plasma concentrations from 6 to 12 hours following dosing. Based on the criteria, I've already dicussed, the 13% difference in AUC would not be considered to be clinically significant. The plasma concentration differences are of somewhat greater importance (Figure 6), however, on further inspection are not as large as the mean data indicate. An unexplained significant period effect was found in this study and the data, when divided into the two treatment periods (Figure 7, Figure 8), reveals that only in period II do the proucts appear to differ and the

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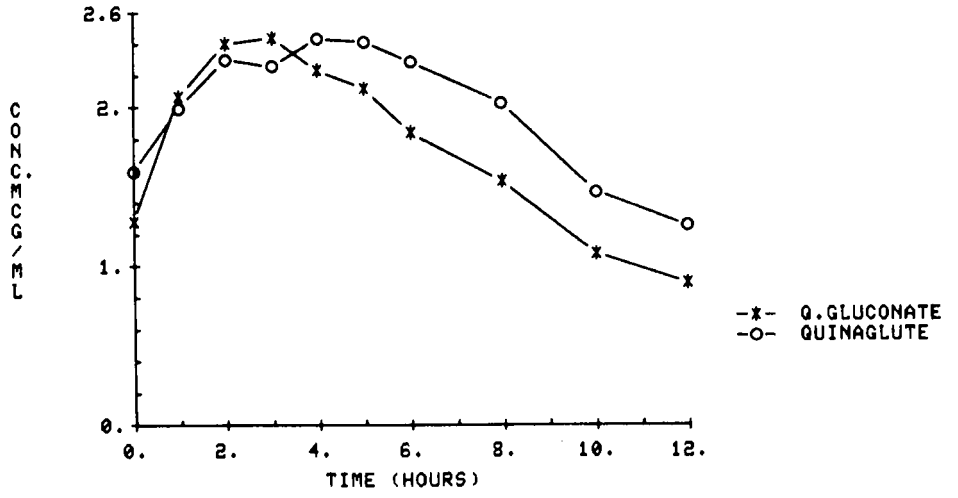

FIGURE 6
Plasma concentrations of quinidine from two controlled-release quinidine gluconate (Data from both treatment periods).

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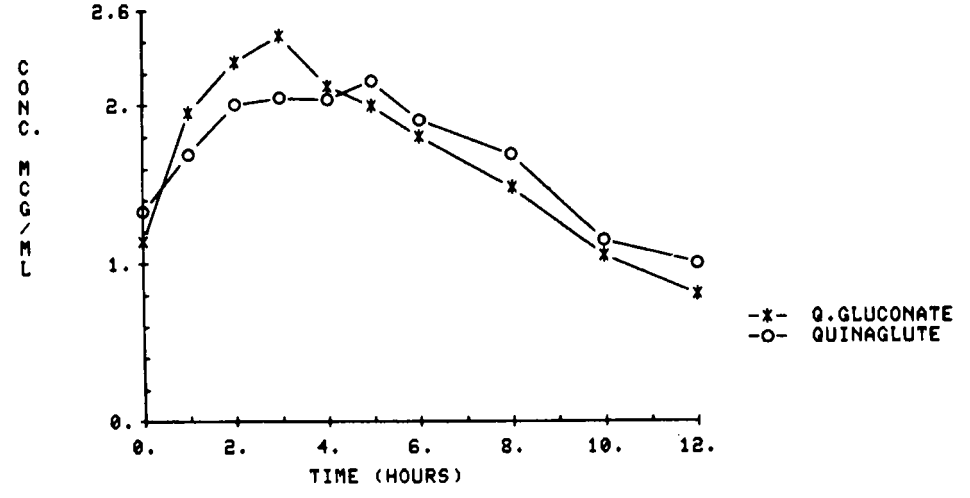

FIGURE 7
Plasma concentrations of quinidine from two controlled-release quinidine gluconate products (Data from period I).

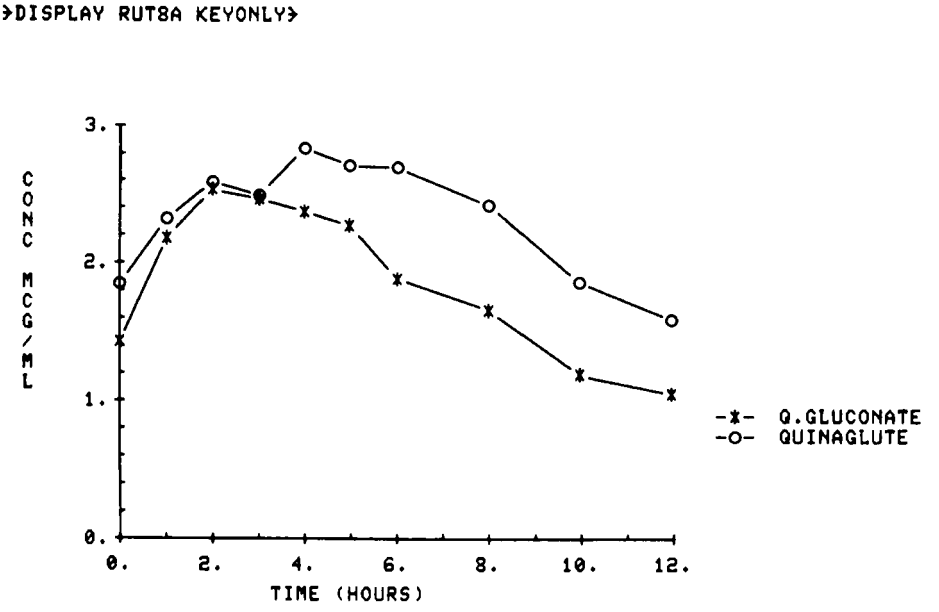

FIGURE 8
Plasma concentrations of quinidine from two controlled-release quinidine gluconate products (Data from Period II).

difference is due primarily to higher levels of innovator product rather than lower levels of the generic product, when compared to the data from period I. With this information, along with the study submitted by the generic manufacturer, we maintain that the two products are equivalent and, in fact, the products are listed as AB on the Approved Prescription Drug Products List meaning that be consider the products to be therapeutically equivalent.

This brings me to the final topic I'd like to discuss, the therapeutic equivalence of oral CR products. Of all the CR products approved by the FDA, only certain quinidine gluconate

and orphenadrine citrate CR products have been listed as "AB" or therapeutically equivalent (TE). Approval of the NDA for a CR product does not necessarily mean a listing of "AB". In order to be TE, the two involved products must, by definition be bioequivalent, that is, have the same rate and extent of absorption. This imposes certain additional restrictions beyond the criteria needed for NDA approval. First, the reference product must be an approved CR product (as contrasted by an immediate release product). Second, the two products' plasma level curves should be essentially superimposable. If these criteria are met, the products will be listed as TE. Unfortunately, this latter condition (superimposition) is sometimes difficult to attain and quantify. Differences in AUC greater than 20% on the mean or failure of 75/75 rule or large differences in CMAX may rule against a listing of TE unless a medical determination is made that these differences should have no effect on therapeutic equivalence of the products. A problem area arises when data fall between these two limits (no differences and relatively large differences) and these products are currently being considered on a case-by-case basis. Additional considerations may enter the picture such as the critical nature of the drug and availability of data from other studies involving the subject CR product and other CR products containing the same drug. We continue to grapple with the question of TE of CR

drug products and I can only caution that the requirements for TE are possibly and probably more stringent than the standards for approval of the bioavailability requirements.

In conclusion, I hope the information that I have presented today serves to clarify the regulatory requirements for the testing of oral CR drug products. I want you to know that we welcome comments and suggestions on the criteria we use in this evaluation. If you have any additional criteria that you feel are of value, please don't hesitate to discuss your ideas with us.