biobatch. These may be selected by using the extremes of the 95% confidence intervals or ±1 standard deviation of the mean plasma level. These curves are then deconvoluted, and the resulting input rate curve is used to establish the upper and lower dissolution specifications at each time point.

In the case of *Level B* and *C* correlations, batches of product must be made at the proposed upper and lower limits of the dissolution range, and it must be demonstrated that these batches are acceptable by performing a BA-BE study.

Immediate-Release Dosage Forms

GENERAL CONSIDERATIONS

Since the mechanisms for release of drug from modified-release dosage forms are more complex and variable than those associated with immediate-release dosage forms, it would be anticipated that an in vitro-in vivo correlation would be easier to develop with the later formulations. Unfortunately, most of the correlation efforts to date with immediate-release dosage forms have been based on the correlation *Level C* approach, although there also have been efforts employing statistical moment theory (*Level B*). Although it is conceivable that the same *Level A* correlation approach may be utilized with immediate-release dosage forms, until data have been gathered to support this concept, *Level B* and *Level C* are the best approaches that can be recommended with these dosage forms.

⟨1090⟩ ASSESSMENT OF DRUG PRODUCT PERFORMANCE—BIOAVAILABILITY, BIOEQUIVALENCE, AND DISSOLUTION

BACKGROUND

This chapter provides recommendations for the in vivo and in vitro assessment of drug product performance. The chapter is intended as a guide to scientists and clinicians seeking to evaluate drug product performance by surrogate procedures correlative and/or antecedent to clinical trials in humans. *USP–NF* provides quality standards for drug substances, excipients, and finished preparations. A *USP–NF* monograph for an official substance or preparation includes the article's definition; packaging, storage, and other requirements; and a specification. The specification consists of a series of universal tests (description, identification, impurities, and assay) and specific tests, one or more analytical procedures for each test, and acceptance criteria. Quality standards are important attributes that must be built into the drug product. Meeting *USP–NF* standards is accepted globally as assurance of high quality and is part of the requirements necessary for approval of a bioequivalent (BE), interchangeable multisource drug product. Multisource drug products must meet certain in vivo and/or in vitro performance standards to be considered therapeutically equivalent and interchangeable. Regulatory approval for interchangeable multisource products may differ somewhat in each country (see the forthcoming chapter *Essentials for Drug Product Selection* ⟨1096⟩ for further discussion). Drug product performance may be defined as the release of the active pharmaceutical ingredient (API) from the drug product dosage form, leading to systemic availability of the API necessary for achieving a desired therapeutic response. This chapter discusses in vivo and in vitro approaches to determining drug product performance. The focus of the chapter is primarily on the performance of solid oral drug products.

The chapter references a Food and Drug Administration (FDA) guidance, *Guidance for Industry—Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations* (2003) (http://www.fda.gov/; search by document title) and a World Health Organization (WHO) document titled *Annex 7 Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability* (2006) (http://who.int/en/; search by document title). FDA guidances are used in the United States; and WHO, FDA, and national/regional guidelines may be used by national/regional drug regulatory authorities. Following approval, control of the quality of a drug product can be achieved in part by the private and/or public specification, which can include a performance test. USP provides the general chapters *Disintegration* ⟨701⟩, *Dissolution* ⟨711⟩, *Drug Release* ⟨724⟩, *In Vitro and In Vivo Evaluation of Dosage Forms* ⟨1088⟩, and *The Dissolution Procedure: Development and Validation* ⟨1092⟩, which describe these tests and procedures.

This chapter provides general information about the conduct of bioequivalence (BE) studies as a surrogate measure of in vivo drug product performance and dissolution profile comparisons as a measure of in vitro drug product performance. The chapter also discusses conditions when an in vivo BE requirement may be waived (biowaiver) for certain drug products and shows how the Biopharmaceutics Classification System (BCS) can be used as a predictor of a drug product's performance. An appendix to this chapter defines key scientific terminology and provides a comparison between FDA and WHO in drug product performance assessment.

BIOAVAILABILITY, BIOEQUIVALENCE, AND DISSOLUTION

Bioavailability (BA) studies focus on determining the process and time frame by which a drug is released from the oral dosage form and moves to the site of action [see FDA Guidance *Guidance for Industry—Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations* (2003)]. BA is an indirect or surrogate measure of the rate and extent to which the API or active moiety is absorbed from a drug product and becomes available at its target sites of action. BA data provide an estimate of systemic drug exposure, including fraction of drug absorbed. For drug products that are not intended to be absorbed into the bloodstream, availability may be assessed by measurements that reflect the rate and extent to which the active ingredient or active moiety becomes available at the sites of action. Drug products are considered BE if a test drug product does not show a significant difference in rate and extent of absorption by comparison with a designated reference drug when administered at the same molar dose of the same active moiety in the same dosage form under similar experimental conditions in either a single dose or in multiple doses.

BA and BE generally can be obtained by serially measuring drug and/or metabolite concentrations in the systemic circulation over a prescribed period. BE studies can use other approaches when systemic drug concentrations cannot be measured or are not appropriate. For these cases, more indirect approaches to BE determination include acute pharmacodynamic endpoints, clinical endpoints, and in vitro studies that typically involve comparisons of the dissolution profiles of test and reference drug products.

BA and BE information are important in regulatory submissions. BA information broadly addresses the absorption, distribution, metabolism, and excretion of the API. For an innovator product, BE studies establish the performance of the product intended for marketing by comparing the bioavailability of the product as developed for marketing approval to the clinical trial material, the drug product used in safety/efficacy trials. For the development and regulatory approval of a generic drug product, the test drug product must be BE to the reference listed drug (RLD) product (usually the brand or innovator drug product that is designated by the applicable regulatory authority).

The ICH document titled *Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (2000) (http://www.fda.gov/; search by document title) provides approaches for setting acceptance criteria for drug product performance. This approach relies on dissolution or disintegration based on clinically acceptable batches, as does FDA's. BE studies focus on the performance of the drug product and usually involve comparisons of two drug products: the test (T) and reference (R) or comparator product. The required studies and the determination of BE are the province of regulatory agencies. In the United States, R is termed the *reference listed drug* (RLD) and is so noted in FDA's *Approved Drug Products with Therapeutic Equivalence Ratings* [*Orange Book* (2008) (http://www.fda.gov/cder/ob)]. To assist countries and regions where the R product may not always be readily identifiable, WHO has prepared a document titled *Annex 11 Guidance on the Selection of Comparator Pharmaceutical Products for Equivalence Assessment of Interchangeable Multisource (Generic) Products* (2005) (http://www.who.int/en/; search by document title). In the WHO document, R is termed the *comparator pharmaceutical product* (CPP). When a country or region has a clearly defined set of CPPs, the task becomes one of requiring that a manufacturer demonstrate, to the satisfaction of its regulatory authority, that its multisource product is pharmaceutically equivalent and BE to the corresponding CPP.

BIOEQUIVALENCE

An interchangeable multisource (generic) product must be pharmaceutically equivalent (PE). The WHO document allows pharmaceutical alternatives to be considered therapeutically equivalent and interchangeable if they are BE. Further, generic products must be shown to be BE in order to be considered therapeutically equivalent (TE) to the R product (CPP). For the product to be considered PE, it must have the same active ingredient, same strength, same dosage form, same route of administration, and same labeling as the comparator product. Several methods exist to assess and document BE. These include the following:

1. *Comparative pharmacokinetic studies in humans.* In these studies, the active drug and/or its metabolite(s) are measured as a function of time in accessible biological fluid such as blood, plasma, serum, or urine to obtain pharmacokinetic measures such as area under the plasma drug concentration vs. time curve (AUC) and maximum concentration (C_{max}) that are reflective of systemic exposure.
   BE studies are designed to compare the in vivo performance of a generic product with an R product. Generally the design is a two-period, two-sequence, single-dose, crossover randomized one carried out in 18 to 36 subjects. The number of subjects should be statistically justified and not less than 12. During the study, blood samples are collected at sufficient intervals for assessing C_{max}, AUC, and other parameters. Blood samples are analyzed using appropriately validated bioanalytical methodology with standard pharmacokinetic measures and statistical approaches. The statistical method for testing pharmacokinetic BE is based on the determination of the 90% confidence interval around the geometric mean ratio of the log-transformed population means (generic/R) for AUC and C_{max} by carrying out two one-sided tests at the 5% level of significance.
2. *Other options.* In addition, comparative pharmacodynamic studies in humans and comparative clinical trials can be used to document or supplement BE assessment. Beyond these clinical studies, in vitro dissolution based on the BCS can ensure BE between T and R products. In vivo documentation of equivalence is especially important for the following: narrow therapeutic range drugs; documented evidence of BE problems; modified-release pharmaceutical products designed to act by systemic absorption; and fixed-dose combination products with systemic action when at least one of the APIs requires an in vivo study.

Immediate-Release Drug Products

Single-dose, crossover BE studies are carried out at the highest dose comparing T and R products under fasting conditions. A parallel study design can be used for drugs that have a very long elimination half-life ($t_{1/2}$). Sampling truncation at 72 hours may be allowable by regulatory agencies. Lower strength(s) of the dosage form can be given a biowaiver based on dosage form proportionality and dissolution profile similarity. Food-effect studies are required if there is an indication in the labeling that concomitant administration of food may diminish, increase, or not influence the BA of the drug product.

Modified-Release Drug Products

BE studies for extended-release dosage forms are carried out as single-dose, crossover studies under fasting and fed conditions at the highest dose to compare T and R products. A single-dose study is more sensitive than multiple-dose, steady-state studies in assessing in vivo drug product performance, particularly with regard to the phenomenon of dose dumping, i.e., the rapid and unintended premature release of the active ingredient from an extended-release product into the bloodstream. Lower strengths of an extended-release dosage form may not require an in vivo study based on use of the same drug-releasing mechanism, dosage form proportionality, and similar dissolution profile.

Orally Administered Drug Products, Not for Systemic Effect

Some oral drug products are intended for local activity. Mesalamine and cholestyramine are examples of drugs that are intended for local activity. For these types of drugs, systemic absorption from the gastrointestinal tract is minimal; thus a comparative clinical trial is required while a systemic drug exposure profile also may be required. In some cases, in vitro studies may be appropriate; such as including comparison of cholestyramine binding to bile salts.

Bioequivalence Studies

Objective—The objective of a BE study is to measure and compare formulation performance between two or more pharmaceutically equivalent drug products. Drug availability from T and R products should not be statistically different when the drug is administered to patients or subjects at the same molar dose under similar experimental conditions.

Design—The design of a BE study depends on the objectives of the study, the ability to analyze the drug (and metabolites) in biological fluids, the pharmacodynamics of the drug substance, the route of drug administration, and the

nature of the drug and drug product. Pharmacokinetic parameters, pharmacodynamic parameters, clinical observations, and/or in vitro studies may be used to determine drug BA from a drug product.

Some possible BE study designs include the following:

1. Single-dose, two-way crossover study under fasted conditions
2. Single-dose, two-way crossover study under fed conditions
3. Single-dose, parallel study under fasted conditions
4. Single-dose, replicate design
5. Single-dose, partial replicate design
6. Multiple-dose, two-way crossover study, fasted conditions
7. Pharmacodynamic or clinical endpoint study
8. In vitro dissolution profile comparisons

The standard BE study is a crossover design (e.g., Latin square crossover design) in which each subject receives the test drug product and the reference product on separate occasions. Studies are usually evaluated by a single-dose, two-period, two-treatment, two-sequence, open-label, randomized crossover design comparing equal doses of the test and reference products in fasted or fed adult healthy subjects. A multiple-dose study may be required for some extended-release drug products. A washout period is scheduled between the two periods to allow the subjects to completely eliminate the drug absorbed from the first dose before administration of the second dose. If the predose concentration is ≤5% of the C_{max} value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations. Samples of an accessible biologic fluid such as blood characterize the drug concentration vs. time profile. During the fasting study subjects are fasted at least 10 hours. A pre-dose (0 time) blood sample is taken. The drug product is given with 240 mL (8 fluid ounces) of water. No food is allowed for at least 4 hours post-dose. Blood sampling is performed periodically after dose administration according to protocol. A food intervention or food effect study is conducted with standard meal conditions that are expected to provide the greatest effects on gastrointestinal physiology so that systemic drug availability is maximally affected. In addition, the high lipid content of the meal may affect the rate of drug release from the product, in situ. A high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively. The drug product is given with 240 mL (8 fluid ounces) of water after ingestion of the standard meal. Subjects should consume identical meals at the same time during a testing period.

Analysis of Samples—Samples, usually plasma, are analyzed for the active drug and, on occasion, active metabolite concentrations by a validated bioanalytical method.

Pharmacokinetic Parameters—Pharmacokinetic parameters are obtained from the resulting concentration-time curves. Two major pharmacokinetic parameters are used to assess the rate and extent of systemic drug absorption. AUC reflects the extent of drug absorption, and the peak drug concentration (C_{max}) reflects the rate of drug absorption. Other pharmacokinetic parameters may include the time to peak drug concentration (T_{max}), the elimination rate constant (k), elimination half-life ($t_{1/2}$), lag time (T_{lag}), and others.

Statistical Analysis

Pharmacokinetic parameters are analyzed statistically to determine whether the T and R products yield comparable values. Because BE studies may use small sample sizes, log transformation of the data allows the frequency distribution of the data to be more normalized so that parametric statistical analyses may be performed (FDA, *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence* (2001) (http://www.fda.gov/; search by document title).

Parametric (normal-theory) general linear model procedures are recommended for the analysis of pharmacokinetic data derived from in vivo BE studies. An analysis of variance (ANOVA) should be performed on the pharmacokinetic parameters AUC and C_{max} using appropriate statistical programs and models. For example, for a conventional two-treatment, two-period, two-sequence (2×2) randomized crossover study design, the statistical model often includes factors accounting for the following sources of variation:

- Sequence (sometimes called Group or Order)
- Subjects, nested in sequences
- Period (or Phase)
- Treatment (sometimes called Drug or Formulation)

The sequence effect should be tested using the [subject (sequence)] mean square from the ANOVA as an error term. All other main effects should be tested against the residual error (error mean square) from the ANOVA. The least-squares means (LSMEANS) statement should be used to calculate least-squares means for treatments. Estimates should be obtained for the adjusted differences between treatment means and the standard error associated with these differences.

The statistical assumptions underlying the ANOVA are as follows:

- Randomization of samples
- Homogeneity of variances
- Additivity (linearity) of the statistical model
- Independence and normality of residuals

In BE studies, these assumptions can be interpreted as follows:

- The subjects chosen for the study should be randomly assigned to the sequences of the study.
- The variances associated with the two treatments, as well as between the sequence groups, should be equal or at least comparable.
- The main effects of the statistical model, such as subject, sequence, period, and treatment effect for a standard 2×2 crossover study, should be additive. There should be no interactions between these effects.
- The residuals of the model should be independently and normally distributed.

If these assumptions are not met, additional steps should be taken prior to the ANOVA, including data transformation to improve the fit of the assumptions or use of a nonparametric statistical test in place of ANOVA. However, the normality and constant variance assumptions in the ANOVA model are known to be relatively robust (i.e., a small or moderate departure from each, or both of these assumptions, will not have a significant effect on the final result). The rationale for log transformation is provided in FDA's Guidance *Statistical Approaches to Establishing Bioequivalence.* Justification should be provided if untransformed data is to be used.

The Two One-Sided Tests Procedure—A testing procedure termed the two one-sided tests procedure is used to determine the comparability of geometric mean values for pharmacokinetic parameters measured after administration of the test and reference products.[1] The two one-sided tests procedure decides whether T is not importantly less than R and whether R is not importantly less than T. Most often, 20% defines an important difference. The statistical procedure involves the calculation of a confidence interval for the ratio (or difference) between T and R pharmacokinetic variable averages. The limits of the observed confidence interval must fall within a predetermined range for the ratio (or difference) of the product averages. Point estimate mean ratios (T/R) derived from the log-transformed AUC and C_{max} data must be between 80% and 125%. Because data are log transformed, T/R = 80/100 = 80% and R/T = 100/80 =

[1] Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J. Pharmacokinetics and Biopharmaceutics,* 1987:15:657–680.

125%. In addition, the 90% confidence intervals for the geometric mean ratios (T/R) for AUC and C_{max} must be between 80% and 125%. The regulatory requirements for the range of 90% confidence intervals for C_{max} may be different in countries outside the United States.

Bio-Inequivalence—The failure to demonstrate BE may be due to a performance failure of the T product or to an inadequate study design. The failure to demonstrate BE due to an inadequate study design can be due to improper sampling in which (1) the sampling time for C_{max} was not properly obtained or (2) the number of samples taken did not adequately describe the plasma drug concentration vs. time profile. Often with highly variable drugs (e.g., %CV >30%), too few subjects were used in the study, and therefore the study was not powered adequately.

Presentation of Data. The drug concentration in biological fluid at each sampling time point should be furnished untransformed for all the subjects who participated in the study. The derived pharmacokinetic parameters also should be furnished untransformed. The mean, the standard deviation, and the coefficient of variation (CV) for each variable should be computed and tabulated in the final report.

To facilitate BE comparisons, pharmacokinetic parameters for each individual should be displayed in parallel for the formulations tested. In particular, for AUC and C_{max}, the difference (T – R), the ratio (T/R), and the log of ratio (log T/R or ln T/R) between the T and R values should be tabulated side by side for all the subjects. For each subject, the summary tables should indicate in which sequence (T, R or R, T) the subject received the product. Histograms showing the frequency distribution of the difference and ln ratio (or log ratio) for the major pharmacokinetic parameters (AUC and C_{max}) are useful in the submission.

In addition to the arithmetic mean for the T and R products, the geometric means (antilog of the means of the logs), means of the logs, and standard deviations of the logs should be calculated for AUC and C_{max}. All means, including arithmetic mean, geometric mean, and means of the logs, as well as standard deviations and CVs, should be included in the report.

DISSOLUTION AND IN VITRO PRODUCT PERFORMANCE

As noted for an official preparation, *USP* monographs provide a public specification that includes a list of tests, references to analytical procedures, and acceptance criteria. Most solid oral dosage forms, including oral suspensions, require a dissolution or a drug release test. Drug dissolution and drug release testing are described in *USP* general chapters *Dissolution* ⟨711⟩ and *Drug Release* ⟨724⟩. These public specifications are used for quality control tests and for market approval. The *USP* dissolution test in the monograph is related to BA and BE only when closely allied with a sound regulatory determination. Without this link it should be regarded solely as a quality control test for batch release. FDA Guidances are (1) *Guidance for Industry—Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (1977) (http://www.fda.gov/; search by document title) and (2) *Guidance for Industry—Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlation* (1977) (http://www.fda.gov/; search by document title).

Dissolution and In Vitro Bioavailability

Drug dissolution and release tests are very useful during drug product development in identifying critical manufacturing attributes such as the impact of ingredient properties and the impact of the manufacturing process on drug product performance. During product development, optimum dissolution conditions need to be developed to discriminate drug product formulations and changes in manufacturing processes. After the finished dosage form is approved for marketing, drug dissolution and release tests are useful in predicting possible changes in performance due to scale-up and postapproval changes (SUPAC). See the following FDA guidances:

Guidance for Industry—Immediate Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (1995) (http://www.fda.gov/; search by document title) and *Guidance for Industry—SUPAC-MR: Modified-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (1977) (http://www.fda.gov/; search by document title).

For some oral drug products, in vitro drug dissolution can be related to in vivo performance, such as bioavailability and/or systemic drug exposure. *USP* general information chapter *In Vitro and In Vivo Evaluation of Dosage Forms* ⟨1088⟩ describes various approaches to in vitro–in vivo correlation (IVIVC).

Dissolution and In Vitro Equivalence

The dissolution test is a powerful in vitro physiochemical test that measures drug product quality and performance for a variety of dosage forms, such as solid oral dosage forms, transdermal dosage forms, suspensions, and certain semisolid dosage forms. The *USP* tests for finished dosage forms can be divided into two types: (1) drug product quality tests and (2) drug product performance tests. Product quality tests are intended to assess attributes such as assay and content uniformity; product performance tests are designed to assess product performance and in many cases relate to dissolution. For details regarding the performance of a dissolution test, see *USP* general chapters ⟨711⟩, ⟨724⟩, ⟨1088⟩, and ⟨1092⟩.

The in vitro dissolution test was initially developed as a quality control tool to ensure drug product quality and batch-to-batch consistency. The test procedures for conducting dissolution tests are described in *USP* general chapters ⟨711⟩ and ⟨724⟩. The development of the BCS brings new understanding and power to the dissolution test. The BCS classifies the drug substance according to the solubility and the permeability of the drug through a biomembrane such as the intestinal mucosal cells. The dissolution rate of the drug from the dosage form is important in substantiating biowaivers based on the BCS.

Dissolution Profile Comparisons

In vitro drug dissolution and release testing can be related to in vivo drug performance, such as BA. The comparisons of dissolution profiles are gaining importance as a means of documenting comparative BA studies—that is, BE. A biowaiver is the replacement or waivers of in vivo BE studies by an in vitro test.

A model independent mathematical approach is used to compare the dissolution profile of two products: (1) to compare the dissolution profile between the T (generic, multisource) product and R (comparator) product in biowaiver considerations; (2) to compare the dissolution profile between the two strengths of products from a given manufacturer; and (3) for SUPAC after the product is approved. For comparing the dissolution profile, the similarity factor f_2 should be computed using the equation

$$f_2 = 50 \cdot \log\left\{\left[1+(1/n)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \cdot 100\right\}$$

where R_t and T_t are the cumulative percentage of the drug dissolved at each of the selected n time points of the reference and test product, respectively. An f_2 value of 50 or greater (50 to 100) ensures dissolution profile similarity and the sameness or equivalence of the two curves, and thus the performance of the two products. At a minimum, three points, no more than one point exceeding 85%, should be used for similarity profile comparison. For products that dissolve very rapidly (≥85% dissolution in 15 minutes) a profile comparison is not necessary.

BIOWAIVER

The term *biowaiver* is applied to a regulatory approval process when the application (dossier) is approved on the basis of evidence of equivalence other than an in vivo BE test. For solid oral dosage forms, the evidence of equivalence is determined on the basis of an in vitro dissolution profile comparison between the multisource and the comparator product.

Biowaiver Based on the Pharmaceutical Dosage Form

A drug product's in vivo comparative BA or BE study requirement may be waived if the products compared contain the same API(s) in the same concentration, contain the same excipients in comparable concentrations, and meet one of the following criteria:

- Aqueous solutions to be administered parenterally
- Solutions for oral use that do not contain an excipient that is known or is suspected to affect gastro-intestinal transit or absorption of the active substance
- Gases
- Powders for reconstitution as a solution
- Otic or ophthalmic products prepared as aqueous solutions
- Topical products prepared as aqueous solutions
- Inhalation products or nasal sprays tested to be administered with essentially the same device. Special in vitro performance testing should be required to document comparable device performance.

Biowaiver Based on Dosage Form Proportionality

When a single-dose fasting BE study is conducted on the designated (usually highest) strength of the drug product, the requirement for the conduct of additional in vivo BE studies on the lower strengths of the same product can be waived, provided that the lower strength (1) is in the same dosage form; (2) is proportionally similar in its active and inactive ingredients; (3) has the same drug release mechanism (for extended-release products); (4) meets an appropriate in vitro dissolution profile comparison criterion (f_2 ≥50); and (5) both lower and higher strengths are within the linear pharmacokinetic range.

Biowaiver Based on the Biopharmaceutics Classification System

The BCS is based on aqueous solubility and intestinal permeability of the API. When the properties of the API are evaluated in conjunction with the dissolution of the pharmaceutical dosage form, the BCS takes into account three major factors that govern the rate and extent of drug absorption from immediate-release dosage forms. On the basis of the solubility and permeability of the dosage form, the drug substance is placed in one of four classes:

Class 1: high solubility, high permeability
Class 2: low solubility, high permeability
Class 3: high solubility, low permeability
Class 4: low solubility, low permeability

Use of the BCS has become a means of documenting BE without the conduct of an in vivo study; see the FDA Guidance *Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (2000) (http://www.fda.gov/; search by document title).

The in vitro dissolution studies are generally carried out by basket method at 100 rpm or by paddle method at 50 rpm (FDA Guidance cited immediately above) or 75 rpm [WHO Guidance, *Annex 7 Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability* (2006)] http://www.who.int/en/; search by document title) in 900 mL of medium at pH 1.2, 4.5, and 6.8. On the basis of dissolution rate, the pharmaceutical dosage forms are classified as (1) very rapidly dissolving, if 85% or greater of the the dosage form dissolves in 15 minutes or less; (2) rapidly dissolving, if 85% or greater of the dosage form dissolves in 30 minutes; or (3) slowly dissolving, if the dosage form takes more than 30 minutes for 85% of drug dissolution.

For biowaiver, the dissolution tests should be carried out for both generic and reference product under the same test conditions. For the generic product to be eligible for biowaiver, the reference product should belong to the same BCS class and should meet dissolution profile comparison criteria. Based on BCS classification and dissolution profile comparison, biowaiver can be considered by regulatory authorities provided the dissolution profile similarity criteria provided in the next sections are met.

Class 1 Drug Products (Allowed in WHO and FDA Approaches)

Dosage forms of drug substances that are highly soluble, highly permeable, and rapidly dissolving are eligible for biowaivers under the following conditions:

1. 85% or more of the dosage form dissolves in 30 minutes or less and the dissolution profile of the generic product is similar to that of the reference product in pH 1.2, 4.5, and 6.8 buffer, using the basket method at 100 rpm or the paddle method at 50 rpm (FDA) or 75 rpm (WHO), and meets the criterion of dissolution profile similarity, f_2 ≥50.
2. If both the reference and the generic dosage forms are very rapidly dissolving (i.e., 85% dissolution in 15 minutes or less in all three media under the above test conditions), then profile determination is not necessary.

Class 2 Drug Products (WHO Approach)

Dosage forms of drug substances with high solubility only in pH 6.8 and high permeability (low solubility by definition, BCS Class 2) are eligible for biowaivers, provided that:

1. The dosage form is rapidly dissolving (85% or more in 30 minutes or less) in pH 6.8 buffer.
2. The generic product exhibits dissolution profiles similar to those of the comparator product in buffers at pH 1.2, 4.5, and 6.8.

Class 3 Drug Products (WHO Approach)

Dosage forms of drug substances that are highly soluble and have low permeability are eligible for biowaivers under the following conditions:

1. Both the reference and the generic dosage forms are very rapidly dissolving (85% dissolution in 15 minutes or less in all three media under the test conditions given above), and they do not contain any excipients

and/or inactive substances that are known to alter gastrointestinal motility and/or permeability or influence drug absorption.

2. Firms should show that the quantity of excipients used is consistent with the intended use. When new excipients and/or atypically large amounts of commonly used excipients are included in the dosage form, additional information documenting the absence of any significant impact on bioavailability of the drug is required.

Dissolution as a Quality Control Test and a BE Test

There is a clear difference between dissolution as a quality control test and dissolution as an in vitro equivalence (BE) test. For immediate-release dosage forms, the quality control test involves a single-point dissolution test in only one medium (generally a compendial test). On the other hand, the in vitro equivalence test (BE test) involves dissolution profile comparison in pH 1.2, 4.5, and 6.8 between the T product and the R product.

APPENDIX

Comparison of FDA and WHO Definitions

Term	FDA	WHO
Pharmaceutical Equivalents	Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, have the same 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 (strength, quality, purity, and identity); but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients, expiration time, and, within certain limits, labeling.	Products are pharmaceutical equivalents if they contain the same molar amount of the same API(s) in the same dosage form; if they meet comparable standards; and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, because differences in the excipients and/or the manufacturing process and some other variables can lead to differences in product performance.
Pharmaceutical Alternatives	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.	Products are pharmaceutical alternative(s) if they contain the same molar amount of the same active pharmaceutical moiety or moieties but differ in dosage form (e.g., tablets vs. capsules) and/or chemical form (e.g., different salts, different esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be BE or TE with the comparator product.
Therapeutic Equivalents	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 labeling.	Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labeling.
Bioavailability (BA)	This term means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.	The rate and extent to which the active pharmaceutical ingredient or active moiety is absorbed from a pharmaceutical dosage form and becomes available [at the site(s) of action] in the general circulation.
Bioequivalent Drug Products (BE)	This term describes pharmaceutical equivalent or pharmaceutical alternative products that display comparable BA when studied under similar experimental conditions.	Two pharmaceutical products are BE if they are pharmaceutically equivalent or pharmaceutical alternatives and their BA, in terms of peak concentration (C_{max}), time to peak concentration (T_{max}), and total exposure (AUC) after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.
RLD (Reference Product) or Comparator Product	An RLD [21 CFR 314.94(a)(3)] means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.	The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product normally will be the innovator product for which efficacy, safety, and quality have been established. The selection of the comparator product usually is made at the national level by the drug regulatory authority.
Generic Product	A generic product is a product that is therapeutically equivalent to the RLD and is intended to be interchangeable with the innovator product.	

Comparison of FDA and WHO Definitions *(Continued)*

Term	FDA	WHO
Multisource Pharmaceutical Products		Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.
Interchangeable Pharmaceutical Product		An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.

⟨1091⟩ LABELING OF INACTIVE INGREDIENTS

This informational chapter provides guidelines for labeling of inactive ingredients present in dosage forms.

Within the past few years a number of trade associations representing pharmaceutical manufacturers have adopted voluntary guidelines for the disclosure and labeling of inactive ingredients. This is helpful to individuals who are sensitive to particular substances and who wish to identify the presence or confirm the absence of such substances in drug products. Because of the actions of these associations, the labeling of therapeutically inactive ingredients currently is deemed to constitute good pharmaceutical practice.

Although the manufacturers represented by these associations produce most of the products sold in this country, not all manufacturers, repackagers, or labelers here or abroad are members of these associations. Further, there are some differences in association guidelines. The guidelines presented here are designed to help promote consistency in labeling.

In accordance with good pharmaceutical practice, all dosage forms [NOTE—for requirements on parenteral and topical preparations, see the *General Notices*] should be labeled to state the identity of all added substances (therapeutically inactive ingredients) present therein, including colors, except that flavors and fragrances may be listed by the general term "flavor" or "fragrance." Such listing should be in alphabetical order by name and be distinguished from the identification statement of the active ingredient(s).

The name of an inactive ingredient should be taken from the current edition of one of the following reference works (in the following order of precedence): (1) the *United States Pharmacopeia* or the *National Formulary;* (2) *USAN and the USP Dictionary of Drug Names;* (3) CTFA *Cosmetic Ingredient Dictionary;* (4) *Food Chemicals Codex*. An ingredient not listed in any of the aforementioned reference works should be identified by its common or usual name (the name generally recognized by consumers or health-care professionals) or, if no common or usual name is available, by its chemical or other technical name.

An ingredient that may be, but not always is, present in a product should be qualified by words such as "or" or "may also contain."

The name of an ingredient whose identity is a trade secret may be omitted from the list if the list states "and other ingredients." For the purposes of this guideline, an ingredient is considered to be a trade secret only if its presence confers a significant competitive advantage upon its manufacturer and if its identity cannot be ascertained by the use of modern analytical technology.

An incidental trace ingredient having no functional or technical effect on the product need not be listed unless it has been demonstrated to cause sensitivity reactions or allergic responses.

Inactive ingredients should be listed on the label of a container of a product intended for sale without prescription, except that in the case of a container that is too small, such information may be contained in other labeling on or within the package.

⟨1092⟩ THE DISSOLUTION PROCEDURE: DEVELOPMENT AND VALIDATION

The USP dissolution procedure is a performance test applicable to many dosage forms. It is one test in a series of tests that constitute the dosage form's public specification (tests, procedures for the tests, acceptance criteria). To satisfy the performance test, USP provides the general test chapters *Disintegration* ⟨701⟩, *Dissolution* ⟨711⟩, and *Drug Release* ⟨724⟩. These chapters provide information about conditions of the procedure. For dissolution, these include information about (1) medium, (2) apparatus/agitation rate, (3) study design, (4) assay, and (5) acceptance criteria. Overall the dissolution procedure yields data to allow an accept/reject decision relative to the acceptance criteria, which are frequently based on a regulatory decision. This chapter provides recommendations on how to develop and validate a dissolution procedure.

GENERAL COMMENTS

The dissolution procedure requires an apparatus, a dissolution medium, and test conditions that provide a method that is discriminating yet sufficiently rugged and reproducible for day-to-day operation and capable of being transferred between laboratories.

The acceptance criteria should be representative of multiple batches with the same nominal composition and manufacturing process, typically including key batches used in pivotal studies, and representative of performance in stability studies.

The procedure should be appropriately discriminating, capable of distinguishing significant changes in a composition or manufacturing process that might be expected to affect in vivo performance. It is also possible for the procedure to show differences between batches when no significant difference is observed in vivo. This situation requires careful evaluation of whether the procedure is too sensitive or appropriately discriminating. Assessing the results from multiple batches that represent typical variability in composition and manufacturing parameters may assist in this evaluation. It is sometimes valuable to intentionally vary manufacturing parameters, such as lubrication, blend time, compression force, or drying parameters, to further characterize the discriminatory power of the procedure.

With regard to stability, the dissolution test should appropriately reflect relevant changes in the drug product over time that are caused by temperature, humidity, photosensitivity, and other stresses.

A properly designed test should result in data that are not highly variable and should not be associated with significant analytical solution stability problems. High variability in results can make it difficult to identify trends or effects of formulation changes. Dissolution results may be considered highly variable if the relative standard deviation (RSD) is greater than 20% at time points of 10 minutes or less and