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Bioavailability And Bioequivalence Assessment in Regulated Market

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Abstract:

Bioavailability is defined as 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. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action. This definition focuses on the processes by which the active ingredients or moieties are released from an oral dosage form and move to the site of action. From a pharmacokinetic perspective, BA data for a given formulation provide an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation when compared to the BA data for a solution, suspension, or intravenous dosage form. In addition, BA studies provide other useful pharmacokinetic information related to distribution, elimination, the effects of nutrients on absorption of the drug, dose proportionality, linearity in pharmacokinetics of the active moieties and, where appropriate, inactive moieties. BA data can also provide information indirectly about the properties of a drug substance before entry into the systemic circulation, such as permeability and the influence of pre-systemic enzymes and/or transporters (e.g., p-glycoprotein).

Key words: ***Bioavailability and Bioequivalence, US FDA, EMA, Health Canada***

Introduction:

BA for orally administered drug products can be documented by developing a systemic exposure profile. A profile can be obtained by measuring the concentration of active ingredients and/or active moieties and, when appropriate, its active metabolites over time in samples collected from the systemic circulation. Systemic exposure patterns reflect both release of the drug substance from the drug product and a series of possible pre-systemic/systemic actions on the drug substance after its release from the drug product. We recommend that additional comparative studies be performed to understand the relative contribution of these processes to the systemic exposure pattern.

One regulatory objective is to assess, through appropriately designed BA studies, the performance of the formulations used in the clinical trials that provide evidence of safety and efficacy. Before marketing a drug product, the performance of the clinical trial dosage form can be optimized, in the context of demonstrating safety and efficacy. The systemic exposure profiles of clinical trial material can be used as a benchmark for subsequent formulation changes and can be useful as a reference for future BE studies.

Although BA studies have many pharmacokinetic objectives beyond formulation performance as described above, but note that subsequent sections of this guidance focus on using relative BA (referred to as product quality BA) and, in particular, BE studies as a means to document product quality. In vivo performance, in terms of BA/BE, can be considered to be one aspect of product quality that provides a link to the performance of the drug product used in clinical trials and to the database containing evidence of safety and efficacy[11].

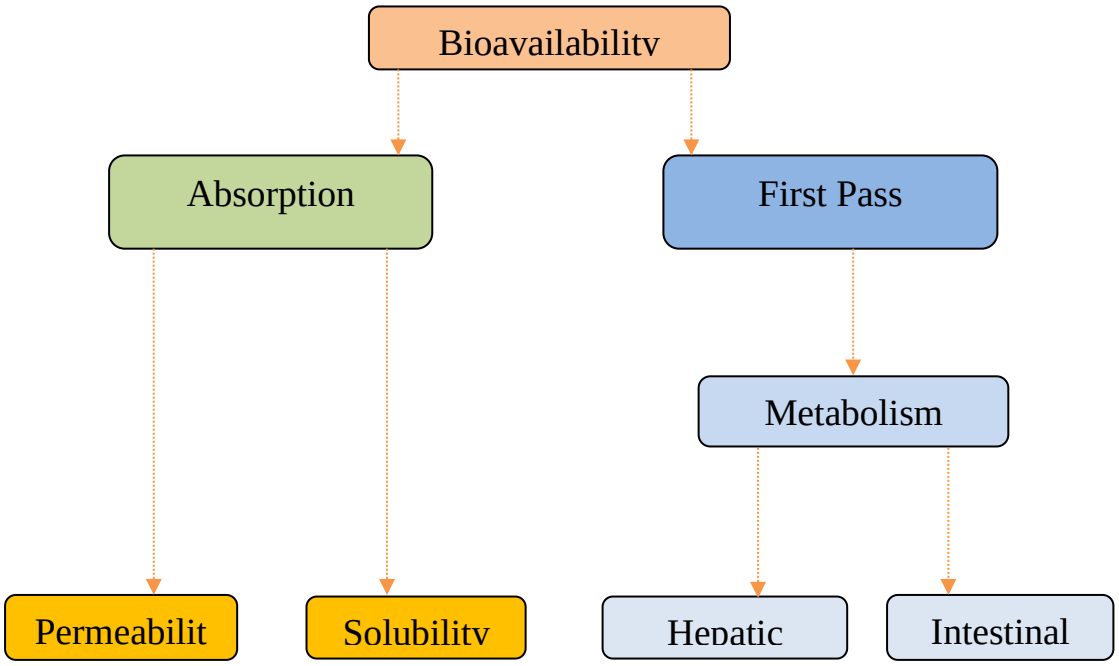

Figure 1: Process of first pass metabolism

BIOEQUIVALENCE

Bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study[10].

As noted in the statutory definitions, both BE and product quality BA focuses on the release of a drug substance from a drug product and subsequent absorption into the systemic circulation. As a result, it recommends that similar approaches to measuring BA in an NDA generally be followed in demonstrating BE for an NDA or an ANDA. Establishing product quality BA is a benchmarking effort with comparisons to an oral solution, oral suspension, or an intravenous formulation. In contrast, demonstrating BE is usually a more formal comparative test that uses specified criteria for comparisons and predetermined BE limits for such criteria.

(a) IND/NDAs

BE documentation can be useful during the IND or NDA period to establish links between (1) early and late clinical trial formulations; (2) formulations used in clinical trial and stability studies, if different; (3) clinical trial formulations and to-be-marketed drug product; and (4) other comparisons, as appropriate. In each comparison, the new formulation or new method of manufacture is the test product and the prior formulation or method of manufacture is the reference product. It is recommended that the determination to redocument BE during the IND period be generally left to the judgment of the sponsor, who can wish to use the principles of relevant guidances to determine when changes in components, composition, and/or method of manufacture suggest further *in vitro* and/or *in vivo* studies be performed.

A test product can fail to meet BE limits because the test product has higher or lower measures of rate and extent of absorption compared to the reference product or because the performance of the test or reference

product is more variable. In some cases, non-documentation of BE can arise because of inadequate numbers of subjects in the study relative to the magnitude of intra-subject variability, and not because of either high or low relative BA of the test product. Adequate design and execution of a BE study will facilitate understanding of the causes of non-documentation of BE.

Where the test product generates plasma levels that are substantially above those of the reference product, the regulatory concern is not therapeutic failure, but the adequacy of the safety database from the test product. Where the test product has levels that are substantially below those of the reference product, the regulatory concern becomes therapeutic efficacy. When the variability of the test product rises, the regulatory concern relates to both safety and efficacy, because it may suggest that the test product does not perform as well as the reference product, and the test product may be too variable to be clinically useful.

Proper mapping of individual dose-response or concentration-response curves is useful in situations where the drug product has plasma levels that are either higher or lower than the reference product and are outside usual BE limits. In the absence of individual data, population dose-response or concentration-response data acquired over a range of doses, including doses above the recommended therapeutic doses may be sufficient to demonstrate that the increase in plasma levels would not be accompanied by additional risk.

Similarly, population dose or concentration-response relationships observed over a lower range of doses, including doses below the recommended therapeutic doses, may be able to demonstrate that reduced levels of the test product compared to the reference product are associated with adequate efficacy. In either event, the burden is on the sponsor to demonstrate the adequacy of the clinical trial dose-response or concentration-response data to provide evidence of therapeutic equivalence. In the absence of this evidence, failure to document BE may suggest the product should be reformulated, the method of manufacture for the test product be changed, and/or the BE study be repeated.

(b) ANDAs

BE studies are a critical component of ANDA submissions. The purpose of these studies is to demonstrate BE between a pharmaceutically equivalent generic drug product and the corresponding reference listed drug. Together with the determination of pharmaceutical equivalence, establishing BE allows a regulatory conclusion of therapeutic equivalence.

(c) Post approval changes

Information on the types of *in vitro* dissolution and *in vivo* BE studies that is recommended be conducted for immediate-release and modified-release drug products approved as either NDAs or ANDAs in the presence of specified post approval changes is provided in the FDA guidances for industry entitled SUPAC-IR: Immediate release solid oral dosage forms: Scale-up and post-approval changes: Chemistry, manufacturing, and controls, *in vitro* dissolution testing, and *in vivo* bioequivalence documentation; and SUPAC-MR: Modified release solid oral dosage forms: Scale-up and post-approval changes: Chemistry, manufacturing, and controls, *in vitro* dissolution testing, and *in vivo* bioequivalence documentation. In the presence of certain major changes in components, composition, and/or method of manufacture after approval, it is recommended that *in vivo* BE be redemonstrated. For approved NDAs, it is also recommended that the drug product after the change be compared to the drug product before the change. For approved ANDAs, it is also recommend that the drug product after the change be compared to the reference listed drug. Under section 506A(c)(2)(B) of the federal food, drug, and cosmetic act, post approval changes requiring completion of studies in accordance with part 320

must be submitted in a supplement and approved by FDA before distributing a drug product made with the change[11].

Table 1: Bioavailability and bioequivalence comparison

Sl. No.	Regulatory body	USFDA 	HEALTH CANADA 	EMEA 
1.	**Standards for BE: Single dose studies**	This guidance recommends that the traditional BE limit of 80 to 125 percent for non-narrow therapeutic range drugs remain unchanged for the bioavailability measures (AUC and C_{max}) of narrow therapeutic range drugs. [90% C.I. of ln-C_{max}, ln-AUC_t, ln-AUC_∞ within 80.00-125.00%. **Additional P.K. Parameters:** AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, λ_z , and $t_{1/2}$]	For drugs with uncomplicated characteristics, the following standards-obtained in single dose cross-over comparative bioavailability studies-determine bioequivalence: a) The 90% confidence interval of the relative mean AUC_t of the test to reference product should be within 80 percent to 125 percent. b) The relative mean measured Cmax of the test to reference product should be between 80 percent and 125 percent.	**AUC-ratio:** The 90% CI for this measure of relative BA should lie within an acceptance interval of 0.80-1.25. In specific cases of a narrow therapeutic range, the acceptance interval may be tightened. In rare cases, a wider acceptance range may be acceptable if it is based on sound clinical justification. **C_{max}-ratio:** The 90% CI for this measure of relative BA should lie within an acceptance interval of 0.80-1.25. The data should be transformed prior to analysis using a logarithmic transformation.
2.	**Standards for BE: Steady state studies**	For steady-state studies, the measurement of total exposure be the area under the plasma, serum, or blood concentration-time curve from time zero to time tau, over a dosing interval at steady state	The relative mean measured Cmax at steady state of the test to reference formulation should be within 80% to 125%. The relative mean measured Cmin at steady state of the test to	Whenever multiple dose studies are performed, it should be demonstrated that steady state has been reached. **P.K. Parameters:** AUC_τ, C_{max}, C_{min}, fluctuation.

		($AUC_{0-\tau}$), where **τ**is the length of the dosing interval. **P.K. Parameters:** C_{min} (concentration at the end of a dosing interval), C_{av} (average concentration during a dosing interval), degree of fluctuation [(C_{max}-C_{min})/C_{av}], and swing [(C_{max}-C_{min})/C_{min}]	reference formulation should not be less than 80%. **P.K. Parameters**: AUC_{τ}, C_{max}, T_{max}, C_{min}, fluctuation. *****For steady-state studies of drugs with uncomplicated characteristics, at least three consecutive pre-dose concentration levels (Cpd) are required to provide evidence of steady state. Generally, observations of Cpd for the test and reference products should be recorded at the same time of the day.	
3.	**Specifics for Modified Release Drugs**	**MODIFIED RELEASE:** For modified-release products submitted as ANDAs, the following studies are recommended: 1] a **single-dose**, nonreplicate, fasting study comparing the highest strength of the test and reference listed drug product and 2] a **food-effect,** nonreplicate study comparing the highest strength of the test and reference product.	**MODIFIED RELEASE** (APPLIES TO SINGLE DOSE): PK Paramètres : AUC_x, AUC_t, AUC_i, AUC_x/AUC_i, AUC_t/AUC_i, C_{max}, T_{max}, λ. For formulations that are likely to accumulate (i.e., $AUC_X/AUC_i < 0.8$), safety requires that steady-state studies be performed in addition to the single-dose studies. Where the AUC_X/AUC_i ratio cannot be reliably	Not applicable

			determined, accumulation must be assumed to occur.	
4.	**Standards for BE: High variability drugs**	Not applicable	Not applicable	**HIGHLY VARIABLE DRUG**: A drug product is called highly variable if it's intra-individual (i.e. *within-subject*) variability is greater than **30%**. 90% CI of AUC ratio: In rare cases a wider acceptance range may be acceptable if it is based on sound *clinical justification*. 90% CI of C_{max} & AUC ratio: In specific cases of a narrow therapeutic range the acceptance interval may be tightened. The interval must be prospectively defined e.g. **0.75-1.33** and justified addressing in particular any safety or efficacy concerns for patients switched between formulations. The interval must be prospectively defined, e.g. 0.75 – 1.33, and justified addressing In particular any safety or efficacy concerns for patients switched between formulations. This possibility is restricted to those products for which at least one of the following criteria applies: **1.** Data regarding PK/PD relationships for safety and

				efficacy are *adequate* to demonstrate that the proposed wider acceptance range for C_{max} does not affect pharmacodynamics in a clinically significant way. **2.** If PK/PD data are either inconclusive or *not available*, clinical safety and efficacy data may still be used for the same purpose, but these data should be specific for the compound to be studied and persuasive. **3.** The reference product has a highly variable within-subject bioavailability. A 'post- hoc justification' of an acceptance range wider than defined in the protocol cannot be accepted.
5.	**Standards for BE: Critical dose drugs**	**CRITICAL DOSE DRUGS**: Unless otherwise indicated by a specific guidance, this guidance recommends that the traditional BE limit of 80 to 125 percent for non-narrow therapeutic range drugs remain unchanged for the bioavailability measures (AUC and C_{max}) of narrow therapeutic range drugs.	**CRITICAL DOSE DRUGS:** 1. The 90% confidence interval of the relative mean *AUC* of the test to reference formulation should be within **90.0 to 112.0%**; 2. The 90% confidence interval of the relative mean measured C_{max} of the test to reference formulation should be between 80.0 and 125.0%. 3. These standards should be met on log transformed parameters	**CRITICAL DOSE DRUGS**: 90% CI of AUC-ratio: In specific cases of a narrow therapeutic range the acceptance interval may be tightened. 90% CI of C_{max}-ratio: In specific cases of a narrow therapeutic range the acceptance interval may need to be tightened.

			calculated from the measured data and from data corrected for measured drug content (percent potency of label claim).	
6.	**Sampling scheme criteria**	That blood samples be drawn at appropriate times to describe the absorption, distribution, and elimination phases of the drug. For most drugs, FDA recommends that **12 to 18** samples, including a predose sample, be collected per subject per dose. This sampling can continue for at least three or more terminal half lives of the drug. At least three to four samples can be obtained during the terminal log-linear phase to obtain an accurate estimate of λ_z from linear regression.	The duration of blood or urine sampling in a study should be sufficient to account for at least 80 % of the known AUC to infinity (AUC_∞). This period is usually at least three times the terminal half-life of the drug. To permit Calculation of the relevant pharmacokinetic parameters, from 12 to 18 samples should be collected per subject per dose. To reduce inaccuracies it is preferable that four or more points be determined during the terminal log-linear phase of the curve.	The sampling schedule should be planned to provide an adequate estimation of Cmax and to cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of absorption. This is generally achieved if the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity. If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples during the terminal log linear phase.
7.	**Long half-life**	LONG HALF-LIFE DRUGS: In a BA or pharmacokinetic study involving an oral product with a long half-life drug, adequate characterization of the half-life calls for blood sampling over a long period of time.	LONG HALF-LIFE DRUGS: For drugs which exhibit a terminal elimination half-life greater than 24 hours, bioequivalence standards in comparative bioavailability studies will be applied to **AUC_{0-72h}**. For the purpose of *bioequivalence*	LONG HALF-LIFE DRUGS: For drugs with a long half-life, relative bioavailability can be adequately estimated using truncated AUC as long as the total collection period is justified. In this case the sample collection time should be adequate to ensure comparison of the absorption process.

			assessment, it will not be necessary to sample for more than 72 hours post-dose, regardless of the half-life. Alternate designs such as parallel studies could be considered.	
8.	**Wash-out**	An adequate washout period (e.g., more than 5 half lives of the moieties to be measured) would separate each treatment.	The interval should be the same for all subjects and, to account for variability in elimination rate between subjects, normally should be not less than 10 times the mean terminal half-life of the drug. (Generally, the interval between study days should not exceed four weeks).	Subsequent treatments should be separated by adequate wash out periods.
9.	**Fasting vs. Fed: Single dose**	FDA recommends a BE study under fed conditions for all orally administered immediate-release drug products, with the following exceptions: • When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I) or • When the dosage and administration section of the RLD label states	For uncomplicated drugs in immediate-release dosage forms, if there is a documented serious safety risk to subjects from single-dose administration of the drug or drug product in the absence of food, then an appropriately designed study conducted in the presence of only a sufficient quantity of food to prevent the toxicity may be acceptable for purposes of BE assessment.	Subjects should preferably be fasting at least during the night prior to administration of the products. If the summary of product characteristics of the reference product contains specific recommendations in relation with food intake related to food interaction effects the study should be designed accordingly.

		that the product should be taken only on an empty stomach.		
10	**Reference Product**	For ANDAs, FDA recommends that the BE study be conducted between the test product and reference listed drug using the strength(s) specified in approved drug products with therapeutic equivalence evaluations (Orange book).	• A drug product that has been issued a notice of compliance pursuant to section C.08.004 of the food and drug regulations, and is currently marketed in Canada by the innovator, or • A drug product acceptable to the Director.	A 'Reference product' must be an 'innovator' product.
11	**Metabolite**	Measurement of a metabolite may be preferred when parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time. If the metabolite contributes meaningfully to safety and/or efficacy.	Determination of bioequivalence should be based on data for the parent drug. Waiver of the measurement of the parent drug will not be considered, unless concentrations of the parent drug cannot be reliably measured, e.g., if the parent drug is not detectable due to rapid biotransformation or limitations in available assay methodology. In such instances, the use of metabolite data may be acceptable.	According to the guideline, the only situations where metabolite data can be used to establish bioequivalence are: 1. "If the concentration of the active substance is too low to be accurately measured in the biological matrix, thus giving rise to significant variability". 2. "If metabolites significantly contribute to the net activity of an active substance and the pharmacokinetic system is non-linear".
12	**Study population**	1] The minimum number of subjects in a cross-over study should be 12. 2] In general, subjects	1] The minimum number of subjects in a cross-over study should be 12. 2] Subjects should be between 18 and 55 years	1] The minimum number of subjects in a cross-over study should be 12. 2] The inclusion/exclusion criteria should be clearly

		should preferably be between 18 - 55 years old and of weight within the normal range	of age. 3] Phenotyping and/or genotyping of subjects can be considered for exploratory bioavailability studies.	stated in the protocol. In general, subjects should preferably be between 18 - 55 years old and of weight within the normal range according to accepted normal values for the '*body mass index'*. 3] Subjects should preferably be *non-smokers* and without a history of alcohol or drug abuse. If moderate smokers are included (*less than 10 cigarettes per day*). They should be identified as such and the consequences for the results should be discussed. 4] Phenotyping and/or genotyping of subjects may be considered for safety or pharmacokinetic reasons.
13	**Bio-waiver**	Separate guideline for the classification and waiver for tests. Follows BCS classification.	Provided specified Bio-waiver for tests and classified the within guideline.	BCS –based bio-waiver classification, provided within the guideline.

Summary & Conclusion

The concept of BE has been adopted by the pharmaceutical industry and national regulatory authorities throughout the world for over 20 years. Because of this, thousands of generic drugs have been manufactured and marketed by the industry after regulatory approval. A lot of advances have been made during these years in developing various approaches to assess BE through research that would assure high quality interchangeable and affordable drugs. However, a lot remains to be done. There is a continuing attempt by national regulatory authorities, international public health organization, pharmaceutical, and basic scientists to understand and develop more efficient and scientifically valid approaches to assess bioequivalence of various dosage forms including some of the tough complex special dosage forms.

The magnitude of assessment of bioequivalence of drug product is influenced by the regulatory environment of the country of marketing. Highly regulated markets have more stringent regulatory policy than countries that are not tightly regulated. Magnitude of regulatory influence is often dictated by the availability of resources,

expertise, and lack of regulation or its implementation. Thus, there is a greater need to harmonize the regulatory environment globally for bioequivalence assessment as far as practicable so that the drug product marketed in different parts and regions of the world would have optimum drug product quality in terms of interchangeability. Proving bioequivalence in various regulatory circumstances without conducting an *in vivo* study is highly appreciated by applicants in order to save relevant resources. Almost two decades ago the BCS based biowaiver was invented as a surrogate for *in vivo* bioequivalence and is now being increasingly utilized. However, divergent requirements in various jurisdictions seem to be still the most relevant reason that the approach is not employed as much as it could be. Obviously, the risk of a failed application and related loss of time on the market do not outweigh pronounced cost savings for generic companies.

When the BE substitution is done by biowaiver the cost reductions are enormous, and is allowed by regulatory authorities $300,000 for a BE study with in-vivo tests compared to $2,000 for a Biowaiver study. Comparison of two different formulations should be done on the basis of dissolution testing, which is basically the same as for the BCS approach. Hence, in vivo pharmacokinetic data can be used as surrogate parameters for in-vivo solubility and permeability data. This thesis aims to substantiate a claim for obtaining biowaivers on the basis of standard human pharmacokinetic data. As, both the BCS and the dose linear pharmacokinetic approach are complementary to each other, and can be used vice versa to support the case for obtaining biowaivers.

When any person is submitting a new drug application, abbreviated new drug application or supplementary new drug application - applicant may ask for a biowaiver from regulatory authorities claiming that the drug/drug product's bioavailability and bioequivalence are self evident. The situations under which BA and BE are accepted as ‘self evident’ is that the drug product contains drug and excipients which are already approved in the same strengths and when:

- The drug product is a parenterals or an ophthalmic or otic solution.
- The drug product is a gas.
- The drug product is a solution, elixir, syrup, tincture, nasal solution, which contains no excipient which may not alter its BE
- The drug product is a solid oral dosage form (other than a delayed release, extended release or sustained release dosage form).
- When the *in vitro* tests have a high level correlation with in vivo tests. Conditions in which BE may be shown by in vitro data in lieu of in vivo data.

The publication of FDA, EU and WHO guidances has had a substantial influence on the implementation of BCS based biowaivers worldwide. A summary of similarities and discrepancies between these major guidances are summarized below:

Table 2: Comparison of FDA, EU and WHO guidance on BCS based biowaiver

Parameters	**FDA**	**EU**	**WHO**
Allowed classes	1	1 and 3	1, 2(weak acids), and 3
High solubility Highest strength completely dissolved in 250mL of aqueous media at 37ºC ±1ºC.			
pH range	pH 1-7.5, and pH = p*K*a, p*K*a±1 (if 3 < p*K*a < 5)	pH 1-6.8, and pH = p*K*a (if 1 < p*K*a < 6.8)	pH 1.2-6.8
High permeability	>90% absolute BA or mass balance study	>85% absolute BA or mass balance study	
Other acceptable methods (the sponsors need to justify the use of these methods)	*in vivo* intestinal perfusion in human *in vivo* or *in situ* intestinal perfusion studies in animal *in vitro* permeation studies using excised human or animal intestinal tissues *in vitro* permeation studies across cultured epithelial cells	None.	*in vivo* intestinal perfusion in humans *in vitro* permeation using excised human or animal intestinal tissue
Rapid dissolution			
Media (studies should /be conducted at 37±1 ºC)	900 mL or less aqueous media (0.1N HCl or SGF; pH 4.5 buffer; and pH 6.8 buffer or SIF)	900 mL or less aqueous media (pH 1.0-1.2 buffer, usually 0.1N HCl or SGF; pH 4.5 buffer; and pH 6.8 buffer or SIF)	900 mL or less aqueous media (pH 1.2 HCl solution; pH 4.5 acetate buffer; and pH 6.8 phosphate buffer)
Criteria	>85% in 30 min in 3 media	Class 1: >85% in 30 min in 3 media (Rapid) Class 3: >85% in 15 min in 3 media (Very Rapid); or, >85% in 30 min and similar dissolution profile to RLD (Similarly Rapid)	Class 1: >85% in 30 min in 3 media (Rapid) Class 2: >85% in 30 min in pH 6.8 medium and similar dissolution profile in 3 media Class 3: >85% in 15 min in 3 media (Very Rapid)
Apparatus (APP)	USP APP I - 100 rpm USP APP II - 50 rpm	Paddle APP - 50 rpm Basket APP-100 rpm	Paddle APP - 75 rpm Basket APP-100 rpm

Other considerations on excipients	Need to justify the use of new excipients or atypically large amounts of common excipients	Class 3: qualitatively And quantitatively the same or similar to RLD	Class 2 and Class 3: qualitative and Quantitative composition will be critically evaluated
Restrictions	Narrow therapeutic drugs Oral products intended to be absorbed in the oral cavity Modified release drug products		

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