

DRUG PRODUCT  
PERFORMANCE-IN VITRO



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# Drug Product Performance



- Drug product performance may be defined as the release of drug substance from the drug product leading to bioavailability of the drug substance the assessment of the drug product performance is important since BA studies are related to pharmacodynamic response and Adverse reactions/events.

# Approaches to Support BA/BE




- In certain circumstances, other approaches are recommended to support a demonstration of BA/BE.
- **In Vitro Tests Predictive of Human In Vivo BA**
- Pharmacodynamic Studies
- Comparative Clinical Studies
- **In Vitro Studies**

## In Vitro Tests Predictive of Human In Vivo BA



- In vitro-in vivo correlation (IVIVC) is an approach to describe the relationship between an in vitro attribute of a dosage form.  
e.g., the rate or extent of drug release and a relevant in vivo response .  
plasma drug concentration or amount of drug absorbed.
- This relationship facilitates the rational development and evaluation of extended-release dosage forms.

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- It (IVIVC) serves as a tool for formulation screening and setting of the dissolution/drug-release acceptance criteria.
  - It is encouraged for all extended release dosage forms (including prototype drugs).
  - In vivo characteristics are determined particularly.
  - When an IVIVC or association is established (21 CFR 320.24(b)(1)(ii)), the in vitro test can serve not only as a quality control specification for the manufacturing process, but also as an indicator of how the product will perform in vivo.

## In Vitro Studies



- BA and BE can be evaluated using **in vitro approaches**. (e.g., **dissolution/drug-release testing**) during the preapproval and postapproval phases ( 21 CFR 320.24(b)(5) and (6)).
- For example, orally administered drugs that are highly soluble and highly permeable, and for which the drug product is rapidly dissolving, documentation of BE using an in vitro approach (**dissolution/drug-release studies**) may be appropriate based on the BCS classification.

## ADDITIONAL INFORMATION ON IN VITRO APPROACHES



- **In Vitro Studies Conducted in Support of a Waiver of an In Vivo BA or BE Data Requirement:**
- FDA may determine that in vitro data are the most accurate, sensitive, and reproducible method to demonstrate BA or BE in other contexts (21 CFR 320.24(b)(5) and (6)).<sup>27</sup> Below stated points provide additional guidance on the conduct of such studies by FDA.





- **Immediate-Release Formulations (Capsules, Tablets, and Suspensions)**
  - i. Over-encapsulation of clinical trial formulations
  - ii. Scale-up and post approval changes.
  
- **Modified-Release Formulations**
  - i. Beaded capsules: lower/higher strength
  - ii. MR dosage forms: lower strength



## Immediate-Release Formulations (Capsules, Tablets, and Suspensions)



If an applicant seeks to demonstrate the BA or BE of immediate-release formulations for capsules, tablets, and suspensions using in vitro data,

### **FDA recommends:**

Sponsors generate dissolution profiles for all strengths using an appropriate dissolution method.

**If the dissolution results indicate that the dissolution characteristics of the product are not dependent on:**

The pH and product strength, dissolution profiles in one medium are usually sufficient to support demonstrating BE.

Otherwise, dissolution data in at least three media (e.g., pH 1.2, 4.5, and 6.8) are recommended.



The f2 test should be used to compare profiles from the different strengths of the product ( FDA guidance for industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms).

An f2 value  $> 50$  : Indicates a sufficiently similar dissolution profile to support a biowaiver.

For an f2 value  $< 50$  : discussion with the appropriate review division is recommended to determine whether an in vivo study is needed. The f2 approach is not suitable for rapidly dissolving drug products (e.g.,  $> 85\%$  dissolved in 15 minutes or less).

# Over-encapsulation of clinical trial formulations

During the course of drug development, sponsors sometimes have to blind the formulations that they use in the clinical trials.

In certain situations, the only difference between the to-be-marketed and clinical trial formulations is that the dosage form is put into a capsule.

This over-encapsulation is done mainly for blinding purposes.

It may be possible to support bioequivalence of the to-be-marketed and clinical trial formulations *using in vitro data only*, provided that no other excipients are added to the capsule and the dissolution profiles are comparable in three media: pH 1.2, pH 4.5 and pH 6.8.

# Scale-up and post approval changes



- Certain formulation changes in components and composition, scale-up, manufacturing site, manufacturing process, or equipment can be made post approval.
- Depending on the possible impact of the manufacturing change on the release of the active ingredient from the formulation and its BA, certain manufacturing changes for IR products can be approved based solely on similarity of the dissolution profiles between the post change and pre change formulations.
- Information on recommendations for using in vitro dissolution and in vivo BE studies for immediate release drug products in such circumstances is provided in FDA's guidance for industry on 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.

# Modified-Release Formulations



- The use of in vitro data may be acceptable for modified-release drug products for which specific postapproval changes are sought is delineated in the FDA 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. The same principles described in the guidance may also apply to preapproval changes.
- Additional considerations for use of in vitro data are described below.



## Beaded capsules: lower/higher strength



- For ER beaded capsules where the strength differs only in the number of beads containing the active moiety, a single-dose, fasting BA or BE study, as appropriate, should be carried out on the highest strength.
- In vivo BA or BE of one or more lower strengths can be demonstrated based on dissolution profile comparisons, with an in vivo BA or BE study only on the highest strength .
- The dissolution profiles for each strength should be generated using the recommended dissolution method.

## MR dosage forms: lower strength



- For MR dosage forms, when the drug product is in the same dosage form but in a different strength and when
- (1) the drug exhibits linear pharmacokinetics
- (2) the various strengths are proportionally similar in their active and inactive ingredients.
- (3) the drug-release mechanism is the same.
- An in vivo BA or BE determination of one or more lower strengths can be demonstrated based on dissolution profile comparisons, with an in vivo BA or BE study only on the highest strength.
- The dissolution profiles for each strength should be generated using the recommended dissolution method.



# 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 during manufacturing.

# Dissolution and In vitro Bioequivalence



- It measures product quality and performance for a variety of dosage forms such as oral dosage forms, suspensions and certain semisolid dosage forms.
- The USP tests for finished dosage forms can be divided into two parts:
  1. Drug product quality test.
  2. Drug product performance test.

## DISSOLUTION PROFILE COMPARISONS

### DEFINITION:

- It is **graphical representation** [in terms of concentration vs. time] of complete release of A.P.I. from a dosage form in an appropriate selected dissolution medium.
- i.e. in short it is the measure of the release of A.P.I from a dosage form with respect to time.

## OBJECTIVE

- To **develop invitro-invivo correlation** which can help to **reduced costs, speed-up product development and reduced the need of perform costly bioavailability human volunteer studies.**
- To stabilize final dissolution specification for the pharmacological dosage form.
- Establish the **similarity of pharmaceutical dosage forms**, for which composition, manufacture site, scale of manufacture, manufacture process and/or equipment may have changed within defined limits.

## IMPORTANCE OF DISSOLUTION PROFILE

- Dissolution profile of an A.P.I. reflects its **release pattern** under the selected condition sets. i.e. either sustained release or immediate release of the formulated formulas.
- **For optimizing the dosage formula** by comparing the dissolution profiles of various formulas of the same A.P.I
- Dissolution profile comparison between pre change and post change products for SUPAC (scale up post approval change ) related changes or with different strengths, helps to assure the similarity in the product performance and **green signals to bioequivalence.**

# Dissolution profile comparisons



- In vitro drug dissolution and release testing can be related related to BA and BE only when closely allied with a sound to in vivo drug performance, such as BA.
- The comparisons of dissolution profiles are gaining importance as a means of guarded solely as a quality control test for batch release. FDA documenting comparative BA studies—that is, BE.
- A model independent mathematical approach is used to for Industry—  
Extended Release Oral Dosage Forms: Develop- compare the dissolution profile of two products: (1) to compare the dissolution profile between the T (generic product and R (comparator) product in biowaiver title)  
(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.

# METHODS TO COMPARE DISSOLUTION PROFILE

## 1) DIFFERENCE FACTOR( $f_1$ )

The difference factor ( $f_1$ ) as defined by FDA calculates the % difference between two curves at each time point and is a measurement of the relative error between two curves.

$$f_1 = \left\{ \frac{\left[ \sum_{t=1}^n |R_t - T_t| \right]}{\sum_{t=1}^n R_t} \right\} \times 100$$

where, n = number of time points

$R_t$  = % dissolved at time t of reference product (pre change)

$T_t$  = % dissolved at time t of test product (post change)



## 2)SIMILARITY FACTOR (F2)

Similarity factor are defined by FDA is logarithmic reciprocal square root transformation of sum of squared error and is a measurement of the similarity in the percentage (%) dissolution between the two curves.

$$f_2 = 50 \times \log \left[ \left\{ 1 + \frac{1}{n} \sum_{r=1}^n w_r (R_t - T_t) \right\}^{-0.5} \times 100 \right]$$

where, n = number of time points

R<sub>t</sub> = % dissolved at time t of reference product (pre change)

T<sub>t</sub> = % dissolved at time t of test product (post change)

## GUIDANCE FOR INDUSTRY

**A specific procedure to determine difference and similarity factors is as follows:**

- Determine the dissolution profile of two products (**12 units each**) of the test (postchange) and reference (prechange) products.
- Using the **mean dissolution values** from both curves at each time interval, calculate the difference factor ( $f_1$ ) and similarity factor ( $f_2$ ) using the equations.
- For curves to be considered similar,  $f_1$  values should be close to 0, and  $f_2$  values should be close to 100.
- Generally,  $f_1$  values up to 15 (**0-15**) and  $f_2$  values greater than 50 (**50-100**) ensure equivalence of the two curves and thus, of the performance of the test (postchange) and reference (prechange) products.
- This model independent method is most suitable for dissolution profile comparison when **three to four or more dissolution time points are available**.

**The following recommendations should also be considered:**

- The dissolution measurements of the test and reference batches should be made under exactly the **same conditions**.
- The dissolution time points for both the profiles should be the same (e.g., 15, 30, 45, 60 minutes).
- The reference batch used should be the most **recently manufactured prechange product**.
- Only one measurement should be considered after 85% dissolution of both the products.
- To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%.
- The mean dissolution values for R can be derived either from
  - (1) last prechange (reference) batch or
  - (2) last two or more consecutively manufactured prechange batches.

## MEETING DISSOLUTION REQUIREMENT

For the selection of the dissolution acceptance criteria ,the following points should be considered,

- The dissolution profile data from the **pivotal clinical batches and primary stability batches** used for setting of the dissolution acceptance criteria of the product .
- Specification should be established based on average invitro dissolution data for each lot under study, equivalent to USP stage 2 testing (n=12)
- For immediate release formulation ,the last time point should be the time point where **atleast 80 % of drug has been released.**
- For extended release formulation ,a **minimum of three time points** is recommended to set the specification .
- The dissolution acceptance criterion should be set in a way to ensure **consistent performance** from lot to lot ,and these not allow the release of any lot with dissolution profiles outside those that were studied clinically.

