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MEETING REPORT

Biorelevant *In Vitro* Performance Testing of Orally Administered Dosage Forms—Workshop Report

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ABSTRACT Biorelevant in vitro performance testing of orally administered dosage forms has become an important tool for the assessment of drug product in vivo behavior. An in vitro performance test which mimics the intraluminal performance of an oral dosage form is termed biorelevant. Biorelevant tests have been utilized to decrease the number of in vivo studies required during the drug development process and to mitigate the risk related to in vivo bioequivalence studies. This report reviews the ability of current in vitro performance tests to predict in vivo performance and generate successful in vitro and in vivo correlations for oral dosage forms. It also summarizes efforts to improve the predictability of biorelevant tests. The report is based on the presentations at the 2013 workshop, Biorelevant In Vitro Performance Testing of Orally Administered Dosage Forms, in Washington, DC, sponsored by the FIP Dissolution/Drug Release Focus Group in partnership with the American Association of Pharmaceutical Scientists (AAPS) and a symposium at the AAPS 2012 Annual meeting on the same topic.

KEY WORDS biorelevant · dissolution · *in vitro* testing · oral dosage forms · quality control

ABBREVIATIONS

AAPS	American association of pharmaceutical scientists
API	Active pharmaceutical ingredient
ASD	Artificial stomach duodenum
BA	Bioavailability
BCS	Biopharmaceutics classification scheme
BE	Bioequivalence
CQA	Critical quality attribute
ER	Extended release
FIP	International pharmaceutical federation

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GI	Gastrointestinal
IR	Immediate release
IVIVC	*In Vitro–in Vivo* rorrelation
IVIVR	*In Vitro-in Vivo* relationship
MR	Modified release
PBPK	Physiologically based pharmacokinetic
PK	Pharmacokinetic
QbD	Quality by design
QC	Quality control
TIM-1	TNO's gastric and small intestinal model

INTRODUCTION

'The FIP Dissolution/Drug Release Focus Group in partnership with AAPS sponsored a symposium on Biorelevant *In Vitro* Performance Testing of Orally Administered Dosage Forms at the AAPS 2012 Annual Meeting in Chicago followed by a 2013 workshop on the same topic in Washington, DC. The objectives of the symposium and workshop were intended to:

- Present the luminal environment and its simulation; discuss advantages and challenges of current methodologies for evaluating the intraluminal performance of orally administered dosage forms and its impact on plasma levels.
- Using case studies, discuss the use of physiological or biorelevant media for formulation selection and optimization during product development.
- Using case studies, discuss the review and utility of biorelevant dissolution studies to assess product performance attributes.
- Present and discuss the ability of current biorelevant dissolution methods to predict *in vivo* performance and/or generate successful *in vitro–in vivo* correlations (IVIVCs) for oral dosage forms.
- Discuss the efforts to improve the *in vivo* predictability of biorelevant tests.
- Summarize current thinking of regulatory agencies on biorelevant performance testing.

This report summarizes discussions and conclusions from both the AAPS symposium and workshop sponsored in partnership with the FIP Dissolution/Drug Release Focus Group. It is published as a symposium/workshop summary report to invite comments from the scientific, technical and regulatory community. FIP plans to co-sponsor an additional workshop in Europe on the topic. Subsequent to the additional workshop, a final position paper including comments on this article will be published.

RATIONALE

During the last 15 years, knowledge of the gastrointestinal (GI) luminal conditions (including the lower gut) has improved dramatically. As a result, various *in vitro* performance tests which mimic the intraluminal performance of orally administered dosage forms, *i.e.* biorelevant tests, have been proposed. Biorelevant dissolution/release testing systems are useful for the evaluation of formulation and food effects on plasma levels after administration of oral dosage forms. Luminal disintegration times of immediate release (IR) dosage forms and the bile acid sequestering activity of resins in the lumen can also be successfully predicted with biorelevant *in vitro* performance testing.

Performance of orally administered dosage forms can be evaluated with *in vivo* studies indirectly (*e.g.* plasma levels) or directly (*e.g.* imaging techniques, sampling from the lumen), and with *in vitro* studies (1,2).

In vivo studies present ethical concerns, high costs, and technical issues. For example, plasma levels are dependent on other factors, such as first pass metabolism and disposition kinetics. Sampling from the lumen is difficult in the fed state and measurement of luminal concentrations with imaging techniques is also challenging. Although animal data are very useful during drug development, animal studies have drawbacks such as their applicability to humans and model restrictions (1). *In vitro* studies are free from ethical constraints and are comparatively less expensive.

An *in vitro* performance test is termed biorelevant when it mimics intraluminal performance of the dosage form. The main hypothesis in the field of biorelevant testing is that the closer the *in vitro* test conditions are to those in the GI tract, the better the chances of predicting intraluminal dosage form performance. However, prediction of dosage form performance may not always require extensive simulation of luminal conditions, *e.g.* when the active pharmaceutical ingredient (API) has high solubility and high intestinal permeability characteristics (3–7).

THEORETICAL PERSPECTIVES

Biorelevant performance testing of orally administered dosage forms typically refers to the evaluation of the release/dissolution of the API from the dosage form and the ability of API to remain in solution and chemically unaltered in the GI lumen, during the entire period of absorption.

Biorelevant dissolution/release testing can be used

- to forecast solubility and dissolution of APIs in the GI lumen, leading to improved API selection (8),

- to forecast the performance of dosage forms in the lumen, leading to improved development (2),
- to build *a priori* models which integrate dosage form performance, drug pharmacokinetic characteristics and gastrointestinal physiology, *i.e.* for streamlining development (9),
- to guide the development of bio-relevant computational models (10) and
- to guide the development of quality control (QC) dissolution tests

Biorelevant dissolution/release testing should take into account hydrodynamic considerations (10) and passage times as well as the composition of the media. Luminal conditions vary a good deal with both the location in the GI lumen and food intake (8). The differences in luminal conditions can be crucial to drug release from IR dosage forms with variable disintegration characteristics (11,12), to poorly soluble APIs (regardless of dosage form type) (13), to modified release (MR) dosage forms (especially the single-unit non-disintegrating forms (14)), and to enabling dosage forms (*e.g.* lipid dosage forms) (15). In such situations, a variety of relevant physiological factors such as pH, buffer capacity, ionic strength and osmolarity, surface tension, micelle formation, digestibility of the dosage form, and the hydrodynamics at the site of release may need to be taken into consideration (16,10).

Two common case situations are discussed below.

Immediate Release Dosage Forms Containing Poorly Soluble APIs

Many newer drugs and drug candidates are poorly soluble and for these, it is necessary to construct appropriate biorelevant tests to forecast dosage form performance. Coupling dissolution kinetics (estimated by using appropriate media and compendial hydrodynamics) with modeling tools can be used to establish a mechanistic link between *in vitro* dosage form behavior and clinical performance (17,18).

Such a link allows formulators and biopharmaceutical scientists to quickly explore "what if" scenarios, to shift dissolution experimentation closer to the clinical level, and to facilitate Quality by Design (QbD) strategies. Mathematical models and computer simulation of the GI environment are playing an increasing role (10,19) in dissolution study and modeling and simulation approaches represent an efficient communication tool to help explain dissolution data across disciplines in drug development teams. Methodologies for developing *in vitro-in vivo* correlations for IR dosage forms have been proposed, but they are not well developed or readily available. Biorelevant dissolution with physiologically based pharmacokinetic (PBPK) modeling represents an alternative approach to get to such IVIVCs (20). This approach potentially allows for combination of data from simpler dissolution assays over use of more complex *in vitro* systems.

Supersaturation and potential precipitation are likely to be factors that influence *in vivo* performance for a high proportion of new oral IR dosage forms based on the 2011 and 2012 new approvals [9 out of 19 and 10 out of 22, respectively (21)]. More work is needed to understand supersaturation/precipitation, especially *in vivo*, and there is a need to consider these aspects in both gastric and intestinal environments. There are virtually no quantitative data on precipitation in the human stomach, for instance. There are also very little data on *in vivo* effects of API permeability (poor *versus* good), of tendency of different APIs for supersaturation (22), of crystalline seeds (nature and amount), of the presence of excipients and food components (may act as inhibitors of precipitation (23)), and, of course, lipid particles that are formed after administration of digestible lipid dosage forms (24).

Many novel *in vitro* models are now available for the evaluation of supersaturation and precipitation, *e.g.* in cases where the transition from the acidic environment of the stomach to the neutral and bile salt-containing environment of the upper intestine may affect the ability of the API to stay in solution. These include the so-called transfer model (25), the artificial stomach duodenum (ASD) model (26), the FloVitro™ model, (27), TNO's gastric and small intestinal model (TIM-1) (28), and others (29). All these methods may provide additional tools to establish an *in vitro-in vivo* link but they require improved verification with *in vivo* data. Eventually, such tests may to be too complex for use as a standard QC release test, but may be used in conjunction with PBPK modeling during dosage form development to demonstrate an understanding of the *in vivo* critical quality attributes (CQAs) of oral dosage forms.

Extended Release Dosage Forms

For many years, correlation of *in vitro* with *in vivo* data of extended release (ER) dosage forms has been based on empirical approaches. Such approaches have been valuable in certain situations.

For ER dosage forms, various sites for release and absorption exist. Therefore, variables, in addition to those mentioned above for IR dosage forms, such as the physical form of the released API [suspension or aqueous (colloidal) solution], luminal transit times, and, for single-unit non-disintegrating dosage forms, stress effects may need to be considered. Unlike with the upper GI lumen, understanding of hydrodynamics is limited with respect to the colon (30). Similarly, although progress has been made regarding the composition of the test medium to be used in *in vitro* studies (31), work still needs to be done for the lower small intestine and also on the importance of regional buffer capacity and ionic strength. These parameters are often critical for the performance of polymers used in

formulating ER products. The vitro release test is the most important test in the development of ER dosage forms, and biorelevant performance testing is a prerequisite for efficient ER product development.

There are various levels for developing a biorelevant release testing method, *i.e.* develop an *in vitro* test that mimics the physiological conditions, develop an *in vitro* test that mimics the *in vivo* dissolution results, model mathematically the relationship between *in vitro* and *in vivo* data, develop a formulation for which the release characteristics are unaffected by lumenal conditions.

PRACTICAL APPLICATIONS

The complex interplay between dosage form factors and gastrointestinal physiology can have a profound effect on the oral absorption and thus bioavailability of orally administered drugs. While many dosage form factors have been traditionally probed *via in vitro* dissolution tools, a connection to clinical impact has not always been attempted. In recent years, the improvement of both biorelevant dissolution methodologies and computational tools with the development of more advanced PBPK models, has led to an increased attention on the use of these tools during dosage form development.

Coupling of dissolution data with modeling tools can help with establishing a mechanistic link between the *in vitro* behavior of the dosage form and the *in vivo* response, allowing pharmaceutical scientists to explore scenarios, eventually to guide the *in vitro* experimentation (typically the *in vitro* dissolution experimentation) to more clinical relevance and to facilitate a QbD strategy. While the development of an IVIVC remains the "gold standard", the new PBPK models provide an alternative means to achieving the translation of dissolution data to clinical relevance, potentially circumventing some of the limitations of traditional IVIVC approaches, especially for IR dosage forms of compounds that belong to Class II or Class IV of the Biopharmaceutics Classification Scheme (BCS).

The combination of dissolution and PBPK modeling data is illustrated in the following study of aprepitant, a low solubility API. *In vitro* data in multiple simulated fluids were generated on drug formulations with micronized and nanosized API. These data were subsequently used as input into a PBPK model to predict PK profiles. The simulation results were shown to accurately predict a food effect for micronized material (32) and the impact of nanosizing the drug (33), when compared to human data (Fig. 1).

Several novel *in vitro* models are now available to evaluate supersaturation/precipitation effects but they need verification with *in vivo* data (*e.g.* 25,26,29). Biorelevant tests are likely to be too complex for use as a standard QC test, but may be used in conjunction with PBPK modeling during product development to demonstrate an understanding of the *in vivo*

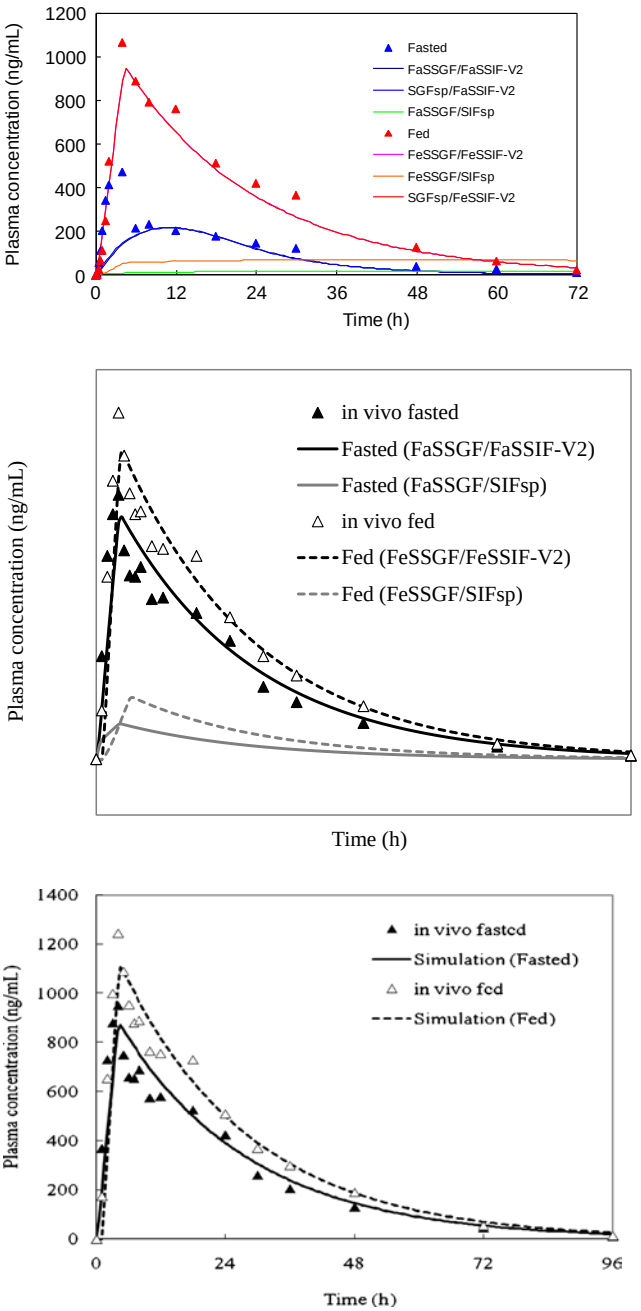

Fig. 1 Comparison of simulation results (lines constructed by using dissolution data from biorelevant and compendial media) with the average *in vivo* results (*symbols*) for a micronized dosage aprepitant formulation 100 mg (*upper graph*) and a nanosized aprepitant formulation 125 mg (*lower graph*) in the fasted and in the fed state (32,33) (reproduced with permission). Key: *FaSSGF* fasted state simulating gastric fluid, *FaSSIF-V2* fasted state simulating intestinal fluid version 2, *SIFsp* USP simulated intestinal fluid without pancreatin, *FeSSGF* fed state simulated gastric fluid, *FeSSIF-V2* fed state simulated intestinal fluid version 2.

critical quality attributes of oral dosage forms. For example, the propensity for a poorly soluble weak base (SB) to precipitate in the upper small intestine was measured *in vitro* with the apparatus schematically represented in Fig. 2. Data from this apparatus were shown to be in line with *in vivo* human data

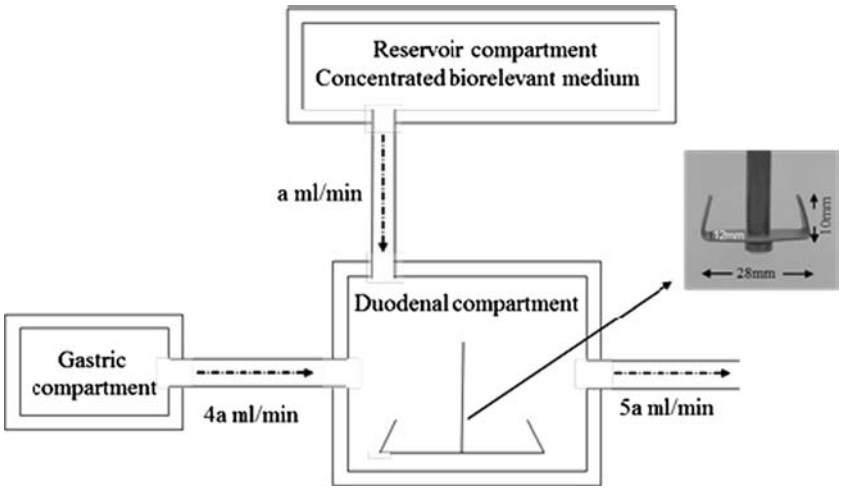

Fig. 2 Schematic representation of a multicompartment system to measure drug precipitation and concentration in duodenum under fasting conditions. Rate of emptying from the gastric compartment changes with time and in order the volume in the duodenal compartment to remain constant the sum of incoming flow rates equal the outgoing flow rate at all times (29) (Reproduced with permission).

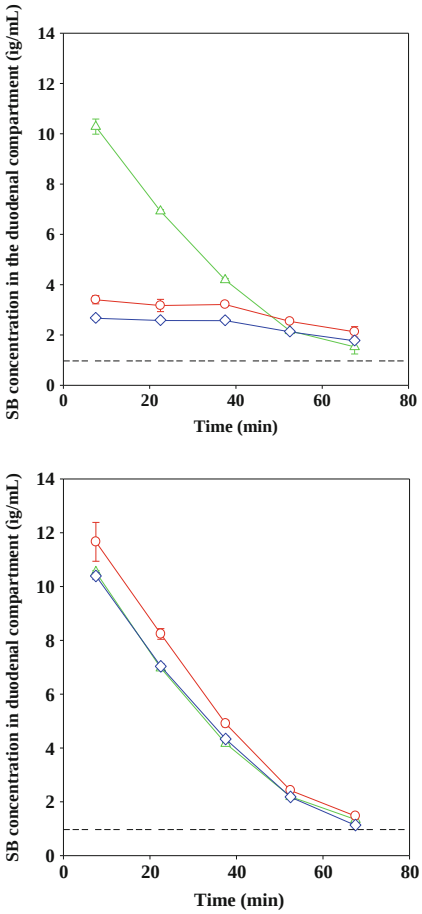

Fig. 3 Simulated duodenal concentrations measured by using the system shown in Fig. 2 for an experimental weak base (SB) showing the importance of solid SB particles on duodenal precipitation after dosing of 100 mg and 400 mg but not after dosing 10 mg SB. *Upper figure*: Concentrations after the initiation of gastric emptying of SB suspensions corresponding to 10 mg dose (*triangles*), 100 mg dose (*circles*) and 400 mg dose (*diamonds*). *Lower figure*: Concentrations after the initiation of gastric emptying of the filtrate of SB suspensions corresponding to the 10 mg dose (*triangles*), 100 mg dose (*circles*) and 400 mg dose (*diamonds*). *Horizontal dotted lines* indicate the value for the equilibrium solubility of SB. (modified from ref 29).

(29) and highlighted the importance of the presence of solid particles on duodenal precipitation (Fig. 3).

Typical approaches to assess *in vivo* performance utilize *in vitro* tests in compendial apparatus. While useful in many cases, the predictive ability of these methods is limited because they do not simulate the varying environment of the human GI lumen. This variation is seen not only in individual subjects throughout the lumen but also between subjects as a result of biological variability. Some of the physiological parameters that are important considerations when simulating the human luminal conditions include: motility (fasting *vs.* fed states), fluid volumes, transit times, pH, osmolality, surface tension, buffer capacity, bile salts, phospholipids, and concentrations of specific ions. A variety of experimental methods have been developed that attempt to simulate these parameters. These techniques range from the relatively simple single compartment systems to complex multi-compartment systems.

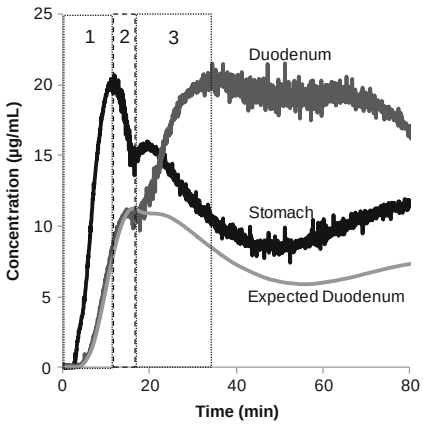

Fig. 4 ASD profiles of drug concentration in the stomach and duodenum showing three distinct phenomena in three different temporal regions: 1) rapid dissolution in the stomach, 2) precipitation in the stomach to a high energy form of the drug and 3) re-dissolution of the high-energy form in the duodenum (42). Reproduced with permission.

The ASD model was developed to mimic the most significant sources of variation in the human GI lumen, namely the transition from the acidic environment of the stomach to the neutral and bile salt-containing environment of the upper intestine. The ASD is a dynamic system where the fluid transport causes a continuous variation in media conditions in the chambers. This condition is more reflective of the *in vivo* conditions and may offer more favorable results when predicting *in vivo* performance compared to some other *in vitro* methods. The ASD is useful to predict performance of formulations as well as mechanistically explain observed performance differences. The importance of simulating this environment dynamically is illustrated in the following study on a solid dispersion dosage form. Figure 4 shows the ASD results which highlight the performance mechanism of this formulation. As can be seen from the stomach concentration profile in Fig. 4, initially the dosage form dissolves rapidly in the stomach to a supersaturated level (region 1), followed by a decrease in drug concentration in the stomach, indicating precipitation to a high-energy form (region 2). The "expected duodenum" concentration can be calculated from the observed stomach concentration data, assuming no additional dissolution or precipitation. Any deviation of the observed from the expected indicates additional dissolution or precipitation in the duodenum. In this case, the observed duodenum drug concentration profile shows that the high-energy precipitate redissolves relatively rapidly in the duodenum (region 3). These phenomena would likely not have been observed with simple one-compartment *in vitro* systems.

Biorelevant *vs.* Quality Control Performance Testing

The benefits for development of clinically relevant *in vitro* test models include the potential direct link to *in vivo* drug behavior. The special apparatus and *in vitro* results must then be leveraged to develop a meaningful QC test. Thus the *in vitro* test for optimization of the dosage form during drug development may differ from the routine QC test for release of the dosage form for clinical studies or for the market. The QC *in vitro* test is primarily intended to demonstrate consistency of the manufacturing process. For routine QC tests, compendial apparatus and physiologically relevant dissolution media are preferred. The QC test should be discriminating and capable of detecting process changes, without being over discriminating to conditions that are actually equivalent *in vivo*. In an ideal case *in vitro* specifications are set in a way that they match the bioequivalence range thus ascertaining that all batches released are bioequivalent. The ultimate goal is to maintain QC methods that are sensitive enough to detect relevant critical process deviations while ensuring consistent quality and performance of dosage forms.

Improved understanding and development of new dissolution technologies has allowed for better predictability of *in vivo* relationships based on *in vitro* results. However, this area continues to require attention in order to deal with the challenges that arise with the application of new technologies in quality control laboratories.

During development of dissolution tests specifically for quality control purposes, it is necessary to understand the characteristics of the API (such as solubility, polymorphism, dispersibility, propensity for precipitation), the characteristics of the dosage form (including excipient properties and, if a modified release dosage form, the drug release mechanism), and any associated risks for variations of the process and product that could have an impact on its quality. A QC dissolution test must be capable of evaluating similarity/differences between batches (before and after process changes when applicable). The method must support specifications for quality control and should link appropriately to clinical studies and/or development dissolution studies.

In summary, the use of a combination of several *in vitro* testing methodologies to assess dosage form performance may be the best approach, as different techniques can provide complementary information. Physiologically relevant media can be used to guide the development of QC dissolution tests, and assess the risk of product changes. More complex biorelevant *in vitro* tests and models are useful tools to investigate dynamic and variable conditions in the GI tract. The combination of biorelevant dissolution testing with PBPK models can provide a mechanistic link between dosage form and clinical performance. This approach can potentially allow for combination of data from simpler dissolution tests over use of more complex *in vitro* systems. From a visionary perspective with full implementation of the QbD paradigm, biorelevant methods that are successfully linked to *in vivo* performance can be used to define critical quality factors and acceptable product design space. These parameters may then be controlled within the manufacturing process rather than as part of end product QC testing.

REGULATORY PERSPECTIVES

Biorelevant *in vitro* performance testing continues to evolve with our increasing understanding and expectations from *in vitro* predictive tests and can serve as a link between the dosage form and its *in vitro* and *in vivo* performance. Biorelevant approaches can be used as learning tools for characterizing the effect of formulation factors on dispersion, dissolution, drug precipitation and stability, and potential interactions between APIs, dosage forms, excipients and the *in vivo* environment. Understanding the factors influencing bioavailability and optimizing the dosage form for improving bioavailability and other aspects of dosage form quality continue to be significant goals of our pharmaceutical community.

Discriminating *in vitro* test methods have significantly enhanced our understanding of *in vitro* and *in vivo* correlations and/or relationships. Sophisticated dissolution test methods and technology including simulated fed and fasted dissolution media for gastric and intestinal fluids have brought in the next phase of biorelevant performance testing. While most IVIVC publications are for extended release dosage forms, application of IVIVC to IR dosage forms is also reported when dissolution is the rate limiting step in absorption of the active moiety. The application of biorelevant methods as learning tools assist in development of IR products by characterizing conditions for optimizing *in vivo* dosage form performance. Developing robust links between the dosage form and its *in vitro* and *in vivo* performance enhances product quality and is expected to result in patient benefit. In addition, these approaches may facilitate leveraging existing knowledge while exploring novel approaches.

Biorelevant *in vitro* release testing may also provide good synergy with QbD in process development where there is an emphasis on linking critical quality attributes and *in vivo* product performance. Clinically relevant dosage form specifications are established when linking the critical quality attributes of a dosage form to its *in vivo* performance (*e.g.* systemic exposure). At the 2012 workshop in Chicago, three approaches were discussed for exploring and establishing clinically relevant dosage form specifications (*e.g.* dissolution acceptance criteria).

In Approach 1, clinical trial batches are used to establish dissolution specification ranges, but no *in vivo* exposure data exist linking dosage form variability to *in vitro* and *in vivo* release characteristics. With this approach, clinical relevance is not always assured and so this approach is least desirable.

For Approach 2, a relationship is developed between *in vitro* release and systemic exposure by manufacturing different dosage form variants with different release characteristics and determining the bioavailability of the variants. Dissolution specifications would then be set to ensure dosage forms have desired *in vivo* performance. For this approach, clinical performance can be assured only for changes within those ranges studied in the bioequivalence (BE) study.

Approach 3 is the most desirable approach and requires development of a validated *in vivo*/*in vitro* correlation model to predict the clinical impact of changes without the need for additional *in vivo* studies. A mechanistic understanding of drug release through risk analysis, design of experiments and development of appropriate design space and control space ensures *in vivo* dosage form performance. However, the conduct of dedicated BA/BE studies during product development to establish the understanding between dosage form variants, release characteristics and systemic exposure is encouraged.

United States of America Regulatory Perspective

The regulatory value of *in vitro* release/dissolution testing is its ability to characterize drug products and assist in decision making including ensuring quality assurance through a linkage to batches used in clinical studies, information on batch to batch consistency, and determining differences in dosage forms. In addition, *in vitro* dissolution testing, as described in guidance documents, can serve as a surrogate for bioequivalence studies to assess impact of post-approval changes and comparison of products from different sources. There are currently no official regulatory definitions or requirements for use of biorelevant media in *in vitro* release testing. Benefits of biorelevant *in vitro* testing as a learning and predictive tool for dosage form characterization, design and performance are recognized. Bioequivalence assessments, by definition are regulatory decision-making tools with established bioequivalence criteria (6,34).

Biorelevant testing may lead to better understanding of *in vivo* performance especially for low solubility drugs (BCS Class II and IV drugs) and may be more valuable in today's drug development environment where the landscape has been shifting to development of a greater number of poorly soluble drugs and more sophisticated dosage forms. Biorelevant approaches can range from using physiologically relevant pH values and standard dissolution apparatus as stated in guidance for industry documents (35) to more complicated media to mimic *in vivo* conditions such as food effects and alcohol dose dumping (*e.g.* 36,37) to combining biorelevant media with novel technologies or novel applications of existing technologies that enable isolated as well as composite assessments of drug release (*e.g.* 14,38,39).

For generic immediate release or delayed release oral dosage forms, often an existing FDA or USP dissolution method is suitable for ensuring drug release, so method development exercises with or without biorelevant media and apparatus are not necessary. The Office of Generic Drugs also tries to achieve consistency in selecting dissolution methods for generic ER dosage forms; however, it may be necessary to develop these methods for ER products on a case by case basis. A variety of conditions can be evaluated during the development of a dissolution method (apparatus, addition of surfactant, stirring speed, pH, volume, medium), and choosing biorelevant options may facilitate understanding and thus development of a method capable of achieving an IVIVR or IVIVC.

European Regulatory Perspective

For European regulators, the term biorelevance is considered to reflect the *in vivo* dissolution behavior of a product (40); hence *in vitro* dissolution should have a relationship to *in vivo* data. However, although biorelevance does not automatically

mean an IVIVC in its strict sense, *in vitro* dissolution methods (*e.g.* for QC purposes) are often unable to demonstrate an obvious relationship to the *in vivo* dosage form performance. Use of different buffers provides biorelevance only in regard to pH and they allow investigating a "worst case scenario". This is because it can be concluded (under strictly defined conditions) that bioavailability differences between two products are not evident if *in vitro* dissolution is similar at pH 1.2, 4.5, and 6.8. However, it is not possible to evaluate the alternative, *i.e.* whether observed *in vitro* differences in these media are relevant *in vivo*, or not. Proposals for considering biorelevant tests in the future have recently started to appear in the literature (41). There is, as yet, no information on biorelevant *in vitro* dissolution tests in the European Pharmacopoeia. Moreover, the regulatory recommendation of achieving sink conditions may sometimes prevent development of most discriminatory and reasonable experimental conditions for *in vitro* dissolution experiments even for QC purposes.

Japanese Regulatory Perspective

Various buffer systems reflecting the luminal pH and various hydrodynamics, with/without the presence of surfactants are suggested as part of the bioequivalence testing procedure for generic dosage forms. According to the Japanese bioequivalence guidelines, not only polysorbate but also sodium lauryl sulfate can be added in the dissolution medium. Based on the experience accumulated over the years, the solubilizing ability of physiologically relevant media may not be high enough for poorly soluble dosage forms to allow comparison of the dissolution profiles between reference and test dosage forms. On the other hand, in the development of the oral dosage forms, physiologically relevant media provide useful fundamental information in evaluating *in vivo* dosage form performance.

OUTLOOK

The way forward for oral dosage form development is to develop *in vitro* tests that are mechanistically, rather than empirically, linked to *in vivo* drug performance. Prediction of kinetics for a new formulation (including potential variability) should be the ultimate endpoint of the evaluation. Thus, in the future it is expected to progress from descriptive pharmacokinetics to PBPK modeling on the one hand, and from "classical" dissolution testing to biorelevant dissolution testing on the other hand. However, in quite a few cases (*e.g.* water soluble drugs in MR dosage forms, just to name one scenario) it is possible to simplify the mechanistic test to attain a workable QC test, and that for other API/formulation combinations a "safe space" can be identified for the dosage form (*e.g.* biowaiver dissolution testing), in which case the quality control test can be greatly streamlined compared to the mechanistic testing performed during development.

For situations where API/formulation combinations are sensitive to the luminal conditions, future objectives should aim at:

- Optimizing existing and/or developing new validated (reproducible and reliable) *in vitro* methodologies. "Methodology" refers to both the specific *in vitro* setup and the data treatment procedure (*e.g.* evaluation of predictability including variability issues). Systematic validation of current methods has just been started by an EU public private partnership project OrBiTo (http://www.imi.europa.eu/content/orbito)
- Gaining better understanding on governing luminal processes in certain case situations
- Decreasing the gap between QC testing and biorelevant testing procedures

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The findings and conclusions in this article have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

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