

GPhA Proposed Pathway for Quality by Design Dissolution Testing and Setting of Specifications for Generic Drugs

**Comments for the Advisory Committee for Pharmaceutical Science
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Introduction

Over the past few years FDA has initiated a number of challenges to the pharmaceutical industry as well as its own scientific staff to move to a quality by design approach for product development and evaluation. The focus of this quality by design approach is based on developing a keen understanding of the formulation, critical manufacturing parameters, rational tests and specifications, among other attributes. Therefore, it is recognized that product design ultimately dictates product specifications. The intent of this document is to provide a proposed rational pathway for developing new dissolution methods for solid oral dosage forms. It does not cover oral suspensions or non-oral dosage forms.

As a result of this initiative, dissolution has become one of the critical tests that require reexamination. Establishing acceptable regulatory dissolution methods and specifications is an area that is problematic for the generic industry. Currently, generic applicants are required to utilize the compendial dissolution method when it exists. For non-USP products, generic applicants are frequently required to use an “OGD” (Office of Generic Drugs) method and associated specifications. Whether the method is a USP or OGD method, it may be ill suited for the particular formulation.

Generic products are often manufactured using excipients that are different than the brand counterpart. Manufacturing processes may also differ significantly. As such, dissolution methods and specifications that are appropriate for the brand product may not be suitable for the generic product and yet the two products are bioequivalent. This has led to significant problems for the generic industry since tests and specifications have been unilaterally imposed in cases for which those tests and specifications are not appropriate. Therefore, moving to a regulatory process that encourages quality by design principles and dissolution methods and specifications that are based on product relevant characteristics is supported by the members of the Generic Pharmaceutical Association.

Please note that these comments are intended to stimulate discussion and consideration by the Food and Drug Administration Advisory Committee for Pharmaceutical Science. Revision and modification to these recommendations may be needed as the dialogue on this topic proceeds.

Rationale for Change

In most cases, dissolution testing is used as a quality control tool to monitor batch-to-batch consistency of the drug release from a product. There are many factors, however, that may affect dissolution tests and results. Each of these factors can lead to variability in test procedures and outcomes leaving questions about a product's quality attributes.

Much attention has been paid to the inherent variability associated with dissolution methodology. During the May 2005 meeting of the Advisory Committee for Pharmaceutical Science, Lucinda Buhse, Ph.D., outlined the variability commonly associated with current dissolution test methods. Examples of such areas of variability include instrumentation, media, degassing, method for sample withdrawal, analysis as well as others. As a result of these variable parameters, the variability in dissolution results may be due to methodology instead of drug product variability.

Additionally, as noted in the introduction, USP or OGD dissolution requirements oftentimes are not appropriate for a particular formulation. As a result, firms may be forced to destroy or recall batches that fail to meet dissolution specifications even though the batch remains bioequivalent and meets all other regulatory standards approved in the ANDA. Therefore, the current system follows a one-size fits all approach. Using scientific evidence based on a drug product to establish methods and set specifications will allow adoption of appropriate dissolution criteria.

One must also consider the result of inherent variability that can be experienced from current methods or uses of methods that are not appropriate for a particular formulation may lead to over-discriminating or non-discriminating dissolution tests and specifications. Therefore, current approaches for dissolution testing clearly have known limitations. Many of these limitations can be addressed by applying more evolved scientific principles inherent with quality by design principles.

Developing a process that considers the critical attributes of each product at the drug development stage and establishing dissolution methodologies and specifications to monitor those attributes is consistent with FDA's desire to have a better mechanistic understanding of the drug product and develop a quality by design approach to dissolution. This approach should also allow for substantial use of prior knowledge of excipients and manufacturing processes in addition to the critical product performance characteristics.

Some of the key underpinnings of a science based approach to dissolution are the design or type of the formulation, such as immediate release (IR), enteric coated, delayed-release, etc., and the biopharmaceutics classification system (BCS). Both of these considerations incorporate important, well-grounded concepts, into the decision making process.

Biopharmaceutics Classification System

While BCS is well established, its principles have not been fully integrated into quality testing schemes. BCS concepts allow a scientifically rational approach to assess whether dissolution testing serves any quality control function at all. For example, for BCS Class I immediate release products, dissolution testing could be unnecessary, thus reducing needless testing and regulatory burden. In other cases, BCS can help determine the proper testing scheme for a product. Therefore, a comprehensive understanding of the critical attributes of a product combined with use of BCS, a change from the current dissolution scheme can be accomplished.

Based on FDA's proposal to move forward with a more scientifically relevant approach for establishing dissolution methods and specifications, GPhA provides specific recommendations in the following section.

Dissolution Testing

GPhA recognizes the complexity of this issue. There are many product specific issues that must be considered in the drug development phase. However, linking product design to setting of specifications should permit development of the most relevant test to assure product quality. GPhA also acknowledges that there may be cases when USP or OGD tests and specifications are appropriate. In these cases the applicant may choose to provide scientific support for adopting those tests and specifications in order to benefit from the regulatory latitude afforded by taking a scientific approach to establishing acceptance criteria for dissolution

As noted above, GPhA recommends that design or type of the formulation and the BCS classifications serve as key determinants in the decision process for dissolution testing. Embodied within these considerations are the primary factors that influence the rate and extent of drug absorption for immediate-release dosage forms. For generic formulations, the dissolution specifications should be based on the performance of batches of the drug product which have been shown to be bioequivalent to the reference listed drug (RLD). A dissolution specification different from the RLD may be set for a generic product, which is bioequivalent to the RLD reflecting the fact that the dissolution is formulation specific.

For the generic industry, the quality by design approach creates the advantage of using "prior knowledge" that might include the following: (a) *in vivo* and *in vitro* performance of the reference product obtainable from the literature and/or experimental studies by the firm; (b) biopharmaceutic, physico-chemical, formulation and dissolution characteristics of structurally related representatives of the same class of drugs. Many generic firms also have a large portfolio consisting of a wide range of product families. This prior knowledge should be leveraged as a resource to aid in the development and justification of tests and specifications for new products.

General Principles of Developing a Dissolution Method

Aspects that may be considered by the firm when developing a suitable dissolution method may include the following:

- The drug is sufficiently stable in the medium/media for the duration and conditions of the dissolution test.
- The drug substance exhibits adequate dynamic solubility in the dissolution medium so as not to unduly limit the dissolution rate under the dissolution test conditions.
- The proposed dissolution medium, volume, and number of dosage units charged into a single dissolution vessel must provide for adequate analytical sensitivity.
- The proposed test or tests should be suitable for all desired strengths of a product.
- The proposed dissolution test must yield a reasonable dissolution rate under reasonable agitation/time conditions.

If, during the development of a dissolution method, a condition is found that does not meet one or more of these requirements, then no further development work should be done on that condition. In other words, a traditional factorial design, in which every possible combination of test conditions is evaluated, is not recommended. For example, if a drug does not exhibit sufficient stability at pH 4.5, then no further work should be done at that pH.

Development of a Dissolution of Generic Drug Product

If there is an available OGD/USP method for a particular product, it can be adopted. However, if this method is not available or if a firm decides to develop an internal method, the applicant should provide scientific justification. (Refer to the Attachment 1 for the Decision Tree)

1. Bioequivalence/biowaiver batches should be used as the basis for justification of the dissolution method.
2. Determine whether the product is an immediate release or extended release product.
3. If the product is an immediate release product, the solubility characteristics of the drug substance should be evaluated. A BCS approach might commonly be chosen.
4. If the drug substance is highly soluble, it should be determined if dissolution testing is appropriate. Alternate approaches such as disintegration or other technology should be justified.

5. If the drug substance is not highly soluble then the development approach should be similar to that for an ER product.(ER development follows)
6. The dissolution profiles should be characterized in multiple media and/or hydrodynamic conditions.
7. Scientific justification should be provided for the dissolution method chosen. Any information about the physical and chemical characteristics of the drug substance and drug product may be provided as supportive scientific information. Any additional information about the manufacturing process may be provided to support the choice of dissolution methods.
8. If the available USP/OGD is the most scientifically justified approach the firm should provide information to support this. This evaluation should provide the same benefits to the firm as any scientifically justified method.
9. Specifications should be based upon sound science principles. Alternate approaches where appropriate (i.e. PAT or disintegration) should be justified.

Setting Acceptance Criteria

The goal or ultimate specification of a generic drug manufacturer is to market a product which is pharmaceutically equivalent and bioequivalent to the reference listed drug. Tests and specifications are put in place to monitor critical product attributes to ensure future batches are consistently manufactured batch to batch.

As outlined above, dissolution may be used as one of these tests. When this is the case, there is no one-size-fits-all approach to setting dissolution specifications. This process will vary from product to product. Dissolution specifications should be set and justified based upon data obtained by the firm. This can include conventional specifications (Q values) and/or adoption of the OGD or USP method. Alternative specifications can be based on scientific rationale taking into account the data generated by the firm. Novel approaches may be developed internally or derived from the scientific literature. Critical performance attributes, implication of in vivo performance, and variability of the biobatch should be considered regardless of the approach. In all cases, the firm will detail their justification in the development report.

One example of a new approach to setting dissolution specifications was put forth by Hauck, et al ⁽¹⁾. The main proposal is that the dissolution specifications should account for variability observed within the exhibit batch. This variability, which for an ANDA is acceptable due to the demonstrated bioequivalence of the batch, is then used as a baseline for future batches. This type of an approach fits well for the generic industry. It allows manufacturers to ensure that variability does not increase to unacceptable levels. Additionally, as process knowledge increases during the life of the product, it sets a path for continuous improvement that can be measured. A firm may decide to proceed further to identify, quantify, and control the individual components of variability. This can include items such as mechanical calibration in lieu of calibrator tablets and Design of Experiments (DOE) to further characterize the process. However, this will be done on a

1 Oral Dosage Form Performance Tests: New Dissolution Approaches, Walter W. Hauck, et al

case by case basis that is consistent with the business model of the firm.

Recommendation

GPhA recommends that FDA carefully consider the comments provided above. GPhA supports adoption of sound scientific principles in developing dissolution methodology and establishing relevant specifications for generic drug products. GPhA believes that the concepts outlined in this document provide a scientifically rational framework for dissolution testing. GPhA looks forward to working closely with FDA in fully developing this framework.

Attachment 1. Decision Tree: Dissolution Specification Development

