

FDA's ACPS Meeting October 2005
Achieving and demonstrating "Quality by Design" with respect to drug release/dissolution performance for conventional or immediate release solid oral dosage forms

Introduction

Drug dissolution or release for most pharmaceutical products containing a drug in the solid state is an essential step in delivering drug molecules to their site(s) of action. Therefore, drug dissolution/release is a critical quality characteristic that needs to be controlled throughout the life-cycle of a product (1).

Over the past three decades, considerable scientific attention has been given to understanding the mechanisms of drug dissolution/release, factors (e.g., formulation, manufacturing process, and physiologic factors) affecting drug release/dissolution, and to establishing standardized methodologies for dissolution testing. Currently a comprehensive regulatory decision system for quality assurance and control of drug dissolution rate of solid oral drug products exists in the form of FDA policy documents on: (a) drug dissolution/release specifications from solid oral dosage forms and establishment of *in vitro* to *in vivo* correlations (2,3), (b) demonstration of drug dissolution/release similarity when formulation and manufacturing changes have to be made (4), and (c) utility of dissolution characterization for obtaining a waiver of *in vivo* bioequivalence studies (5). Furthermore, the ICH Q6A guideline on establishing specifications has also been developed that addresses many aspects of dissolution specification setting (6).

At the May 2005 meeting of the ACPS we proposed that significant opportunities exist to further improve the effectiveness and efficiency of dissolution rate control and related regulatory decisions by building upon the current regulatory decision system. These opportunities are afforded by: (a) the ability to utilize pharmaceutical development information in ICH Q8 (7) in regulatory decisions and (b) the availability of new technologies for more effective control of formulation and manufacturing variables that impact drug dissolution process (8). We believe that realizing these opportunities can significantly improve FDA's ability to assure quality, create regulatory flexibility (e.g., by reducing regulatory reporting requirements) for continuous improvement, facilitate introduction of innovative and more efficient control systems, and reduce waste and unnecessary costs in the current system. The FDA proposal – tactical plan – outlined the following steps as a means to further enhance the effectiveness and efficiency of the current regulatory decision system:

1. Develop an alternate regulatory approach to dissolution method validation, without the need for an external calibrator tablet, that provides for assessment and control of all relevant sources of variability in the measurement system.
2. As part of Step 1, above, or as an independent step, develop an approach to utilize the pivotal clinical trial product or the pivotal bio-batch to (a) characterize reproducibility and repeatability (e.g., DOE based Gauge R&R for destructive samples) of the measurement system and (b) to define criteria

when this study can also serve to benchmark “acceptable” total variance (product + measurement system) in absolute terms as well as in an appropriate relation to some appropriate measure of clinical, pharmacodynamic, or pharmacokinetic variability. Identify experimental designs and/or other information (e.g., from routine production operations) that may allow robust estimation of product variance. In conjunction with subsequent steps listed below, outline how structured formulation development information can support development of a rational Gauge R&R protocol and also further assist in reducing regulatory concern on benchmarking “acceptable” variability in pivotal clinical trial product.

3. Develop a comprehensive (systems-based) decision tree approach for establishing the dissolution specification (assuming availability of structured pharmaceutical development information as outlined above). Compare the proposed decision tree to the current ICH Q6A decisions trees and articulate the advantages and limitations of these two approaches.
4. In conjunction with Step 3, identify and define opportunities for utilizing the PAT approach for controlling dissolution rate and development of real time quality assurance strategies.
5. Develop a decision tree for the “design space” concept articulated in the draft ICH Q8 (see 23) to minimize the need for regulatory application commitments on process parameters and manufacturing options (i.e., in-process controls for appropriate material attributes).
6. For both new and generic drug applications, develop a side-by-side comparison of the proposed regulatory decision process with the current decision process for dissolution specifications and post approval change management. Provide justification and explain why the level of confidence (with respect to quality assurance and control of drug dissolution rate) under the proposed approach should be higher than what is achieved under the current system.
7. Seek ACPS recommendation at the May 2005 meeting on general considerations for identifying and developing statistical analysis procedures to support the Steps above.
8. Based on recommendations of the ACPS at the May 2005 meeting, develop a detailed proposal for Steps 1-7 and seek to establish consensus on the detailed regulatory decision criteria at a subsequent meeting of the ACPS.
9. Seek harmonization on the approach (Step 8) with other regulatory authorities, specifically in the ICH regions.

At the May 2005 meeting in our presentation we had extended invitations to all stakeholders to consider our proposed tactical plan as a first step and to develop their own proposals for addressing the challenges and opportunities identified by way of the ACPS discussions. Both innovator (PhRMA) and generic (GPhA) trade associations, and the USP, are planning to present to you their perspectives and proposals at the October 2005 meeting. We also have received a report on dissolution test variability from two academicians and we have included this report in the background packet. An FDA working group has been working to further develop the proposed tactical plan and will

present their expanded proposal. We also plan to study the summaries of proposals from the stakeholders and identify areas of agreement, and to develop scientific arguments where an agreement is not reached.

In this document we will attempt to articulate some of the key challenges (i.e., opportunities for improvement and reducing uncertainty to make proactive decisions) and provide a context using a current regulatory decision process – establishing dissolution specification for a generic immediate release (IR) solid oral drug products (e.g., tablets and capsules). The underlying principles discussed are also applicable to new drugs. Note that the term specification includes the attribute, the test method and the acceptance criteria. We hope this example will help you critically evaluate the proposal that will be presented to you in October 2005.

Dissolution rate specification for an IR generic product

Establishment of dissolution rate specification for an IR generic product is based on a demonstration of acceptable bioequivalence between a generic bio-batch (generally manufactured at 1/10 the commercial scale) and its Reference Listed Drug (RLD) product. The current regulatory process is depicted in the process flow chart below (flow chart symbols selected, such as “pre-defined process”, are also identified to distinguish this from a decision tree). Note that this process does not specifically identify the option reserved by the Office of Generic Drugs to request submission of additional dissolution testing data as a condition of approval, when such requests are scientifically justified (2).

In summary, the current process is predominantly based on the existence of a compendial dissolution specification (for RLD) and is generally efficient if the follow-on generic product conforms to this specification (i.e., the same test method and acceptance criteria). In the absence of a compendial specification, a generic product would be expected to utilize the same test method as the RLD if information about this method is publicly available. A different, “discriminating”, dissolution test method can be justified for a generic product when its dissolution profile is substantially different compared to its RLD (note that its in vivo performance in a bioequivalence trial should be acceptable). The acceptance criteria for a generic product using the RLD method, or a different method, are established based on available dissolution, bioequivalence and shelf-life data (2).

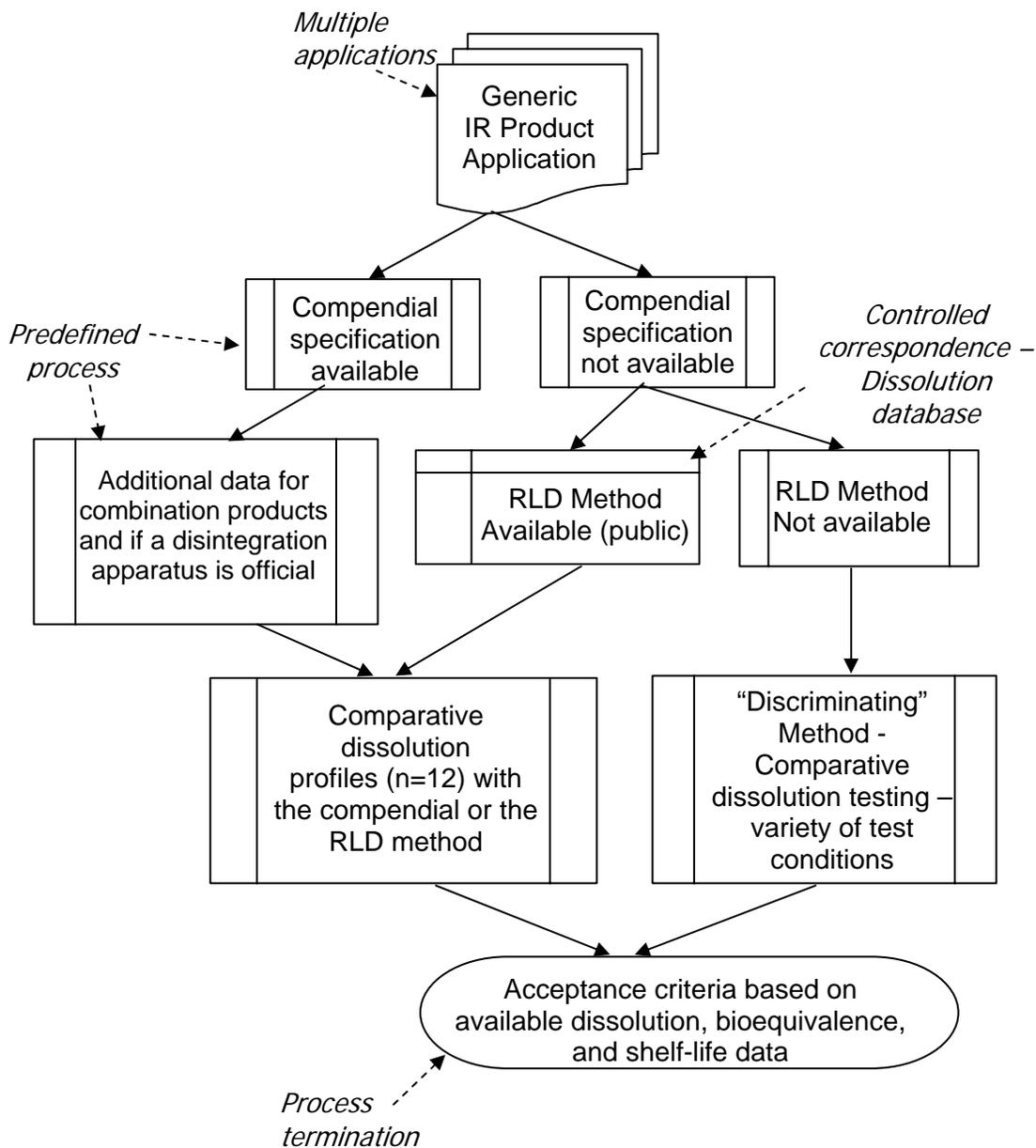


Figure 1. Regulatory process flow chart for dissolution rate specification setting for an IR oral generic drug product that has successfully demonstrated bioequivalence to the RLD (2).

For most conventional IR products, this process works well. However, in some cases the following challenges are observed:

- A focus on compendial standards/specifications. For a composite physical functionality, such as dissolution, which is influenced by many physical factors, such as hydrodynamics (see attached report submitted by Prof. Piero Armenante and Prof. Fernando Muzzio, "Inherent Method Variability in Dissolution Testing: The Effect of Hydrodynamics in the USP II Apparatus"), and the inherent

variability in these factors, a compendial method and acceptance criteria optimally defined for an originator or RLD product may not be optimal on products that follow-on (with different formulation and manufacturing process design). This challenge is expected to increase with increasing complexity of product designs and is clearly more significant for modified release dosage forms (that are often designed with a different drug release mechanisms).

- The administrative, and in some cases the legal, process to address this challenge can be significant and can delay approval of a generic drug application
- This approach may also increase the likelihood of approving a generic product with sub-optimal dissolution specification that can
 - lead to frequent out-of-specification deviations and batch rejections, and/or
 - result in approval of a generic product with an inadequate specification for assuring unchanged product quality and performance over its life-cycle; the possibility of such an outcome may be illustrated by the difference in approaches to dissolution testing and specification setting used by the US and Japan (9).
- A desire to achieve method consistency through an insistence on the RLD method. The challenges outlined above are also applicable in this instance. Clearly, method consistency has its advantages from a laboratory resource and quality management perspective; however, when dealing with composite physical attributes and their test methods (as opposed to a chemical test based on separation science), the broad applicability of such test methods to different formulations and product designs (e.g., mechanism of release) needs to be considered carefully. In the current system, it may be easier to overlook such considerations when doing so increases administrative and regulatory procedural uncertainty.
- The desire to develop a “discriminating” test method. Any good analytical test method should be able to clearly distinguish between unacceptable and acceptable quality products. The goal of “discriminating” dissolution test conditions are just that: to ensure an ability to distinguish between acceptable (i.e., acceptable bioavailability as demonstrated via bioequivalence assessment) and unacceptable lots of an approved product over its intended shelf-life. The approach for identifying “discriminating” dissolution test conditions is based on product lots used for bioequivalence evaluation or clinical trials. Individual units are tested under conditions differing in, for example, pH of the dissolution media and speed of rotation of the paddle or basket assembly of a selected dissolution apparatus. Test conditions that exhibit a large difference in dissolution rate (within a bio-batch or between clinical batches) are generally considered to be “discriminating” and are selected for a “discriminating” test method since this approach is able to show a large difference among individual units from clinically acceptable batches or a bio-batch used to demonstrate bioequivalence –*“Very often, the in vitro dissolution test is found to be more sensitive and discriminating than the in vivo*

- test. From a quality assurance point of view, a more discriminative dissolution method is preferred, because the test will indicate possible changes in the quality of the product before in vivo performance is affected” (2).*
- Structured pharmaceutical development information (as outlined in ICH Q8) is generally not uniformly available during the regulatory review process. Regulatory decisions on dissolution test methods and acceptance criteria are, therefore, predominantly based on limited manufacturing experience and data. Only on rare occasions are dissolution data from lots that have unacceptable bioavailability shared in regulatory applications. Historical experience suggests that for most IR dosage forms an *in vitro to in vivo correlation* is either not expected (i.e., dissolution process *in vivo* is not rate limiting) or that reliable correlations are difficult to establish due to inherent (*in vivo*) variability.
 - These observations (listed above) and the process by which the inherent variability in the current dissolution method is managed (system suitability based on a calibrator tablet as discussed at the May 2005 ACPS meeting), raise important questions - What is the “discriminating” test method discriminating? And, what is the clinical relevance of what the test is discriminating?
 - Are the differences observed due to product quality differences (note – lots used in these experiments are generally those that are used to establish bioequivalence or clinical safety and efficacy), or are these differences due to differences in variability induced by the dissolution test conditions?
 - From both a scientific and public health perspective (including the efficiency of pharmaceutical manufacturing and the associated cost implications), it is important to adequately address these questions.
 - Establishing acceptance criteria using a “discriminating” test method. For IR products, generally, a one point acceptance criterion is established, with some exceptions, in which case a two point acceptance criteria is established. In general, preference is to set a lower limit for % dissolved (“Q”) at or above 70% of the labeled dose, coupled with a time point when this % dose is dissolved (e.g., 15, 30, 45 or 60 minutes). Often this decision is subject to significant debate and discussion between FDA and an applicant. Although, the issues of dissolution sample size and sampling (to be representative of a batch) have not been the subject of debate at the same level as for blend content uniformity, it does play a role in dissolution specifications setting. A general regulatory preference is to establish an acceptance criteria that will trigger the “Stage 2” of the dissolution test (n=12; see table below). This is in part due to a concern that a sample of n=6 may not be sufficient to represent an entire batch of tablets (generally a million or more units). Note that issues related to sampling plans to ensure that collected samples are “representative” of batch is a “cGMP issue”, and how this is accomplished is generally not known to the CMC and Bio review staff who establish the specification. Absence of this information may be a contributing factor to the “small sample size” concern.

Stage	# Units Tested	Pass If
1	6	No dosage unit is less than $Q + 5\%$
2	6	Average of 12 units $\geq Q\%$ & no dosage unit is less than $Q-15\%$
3	12	Average of 24 units $\geq Q\%$ & no more than two dosage units are less than $Q-15\%$ & no dosage unit is less than $Q-25\%$

- This approach to establishing acceptance a criterion focuses on the mean value and addresses variability indirectly using the “Stage” concept described above. As a result, robust estimates on variability are not obtained.
- Without robust estimates of variability and the knowledge of factors contributing to observed variability, a move towards statistical process control is not feasible.
- Furthermore, since a high degree of uncertainty exists with respect to “What is the “discriminating” test method discriminating?” it sets up the challenge eloquently articulated by Dr. Woodcock - “*..the limits on quality attributes are often chosen empirically to ensure production of batches that resemble the batches tested in the clinic. However, this approach will only ensure consistent clinical performance if the relationship between those limits and the clinical outcome is understood. Without this understanding, the limits could be overly wide, unnecessarily tight, or completely irrelevant to clinical performance. Even worse, other, critically important attributes may not be identified, measured and controlled*” (1).
- During routine production, when *out-of-specification* (OOS) results are obtained it is often difficult to identify *root cause* and to implement an effective *corrective action – preventive action* (CAPA) plans. Investigations into OOS observations (often recurring) take significant time and resources, which in turn contribute to the low efficiency in the current system. At the end of such an investigation it is often concluded that the “*root cause is unknown*” (and the batch is generally rejected) or the blame is directed to an analyst - “analytical error”.
- Validation of dissolution test method. The FDA guidance (2) outlines the following steps for “validating” the dissolution apparatus/methodology.
 - the system suitability test using calibrators;
 - deaeration, if necessary;
 - validation between manual and automated procedures; and
 - Validation of a determinative step (i.e., analytical methods employed in quantitative analysis of dissolution samples). This should include all appropriate steps and procedures of analytical methods validation.

- The first step to demonstrate suitability of a dissolution apparatus - based on calibrator tablets - was extensively discussed at the May 2005 meeting and the committee was unanimous in its recommendation that FDA should develop an alternative approach which is not based on a “calibrator tablet”.
 - The impact of this step, and why an improved alternate approach is essential, is apparent when we examine the expected dissolution rate acceptance criteria (Stage 2, n=12 and no dosage unit is less than Q -15%) and the instrument suitability criteria based on dissolution rate of a calibrator tablet (Prednisone 10 mg Lot N: 54-78% (apparatus 1) and 28-54% (apparatus 2); Lot O0C056: 51-81% (apparatus 1) and 26-47%) (10). Furthermore, this approach confounds the drug product variability with the variability for calibrator tablets.
- The steps outlined above describe the current regulatory decisions process for establishing dissolution rate specifications - “*In vitro dissolution specifications are established to ensure batch-to-batch consistency and to signal potential problems with in vivo bioavailability*” and “*once a dissolution specification is set, the drug product should comply with that specification throughout its shelf life*” (2).
 - Justifying that a dissolution test and acceptance criteria is appropriate to establish shelf-life can also pose significant challenges since information on failure modes and degradation mechanisms are not available in regulatory submissions.
 - Product characterization (e.g., multiple dissolution profiles generated under different conditions) to demonstrate “unchanged” quality, when post-approval changes (e.g., scale-up) have to be made, also poses significant challenges. We often do not have a means to evaluate the clinical impact of when observed differences in dissolution profile (point-point comparison of % dissolved at 3 or more time points) are greater than 10-15%. In such cases, we often have to request *in vivo* bioequivalence demonstration.

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