Advisory Committee for Pharmaceutical Science, CDER, FDA May 2005

Quality-by-Design Approach for Regulatory Decisions: Seeking Applications for Establishing Drug Dissolution/Release Specifications, Creating Flexibility for Continuous Improvement and for Assessment of Therapeutic Equivalence

Background

Progress on articulating the "desired state"

Over the past four years FDA initiatives on Process Analytical Technology (PAT) (1) and CGMP's for the 21st Century (2) have been developed with the goal of providing a broader systems perspective for regulatory decision making and to facilitate introduction of new scientific opportunities for improving the efficiency of pharmaceutical product development and manufacturing processes. The PAT definition and principles of *quality-by-design* (QbD) outlined in the FDA's PAT guidance (3) have also been incorporated in the draft *ICH Q8: Pharmaceutical Development* guideline [4]. With this accomplishment, significant progress was achieved in articulating a shared vision for the future or the "desired state" in the three regions – U.S., Europe, and Japan. This vision was articulated as follows:

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- An ability to effect continuous improvement and continuous "real time" assurance of quality

This description of the "desired state" aims to enhance the utility of product and manufacturing process design knowledge and understanding in regulatory quality assessment process. It is proposed that when product and process knowledge and understanding are shared with FDA, it can provide a basis to recognize the level of understanding achieved, facilitate risk-based regulatory decisions, and provide flexibility for continuous improvement for companies that have demonstrated an ability to manage risk to quality [5]:

- Regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability,
- Risk-based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product.

Industry Concern "Regulatory Uncertainty"

To-date, ACPS discussions on the topic of Quality-by-Design (QbD) have essentially focused on the conceptual framework which the committee strongly endorsed. Some members of the committee have pointed out that QbD principles are well established and are being practiced by several industrial sectors. Discussion with several pharmaceutical companies suggests these concepts and principles are in practice, to different degrees, within the pharmaceutical industry. However, industry continues to express a concern of "delayed approval" if they include pharmaceutical development information in their regulatory application. It should be noted that pharmaceutical development information is an integral part of regulatory applications in Europe; therefore, this concern, in part, is probably reflecting the challenge of scientific communication across disciplinary boundaries. Other factors may include a lack of appreciation on the part of R&D and Regulatory Affairs departments (generally responsible for regulatory application submissions) of the challenges faced in day-to-day manufacturing operations and the substantial amount of wasted resources contributing to the high costs [5].

Reducing Uncertainty

From an FDA review perspective, currently available data in new and abbreviated new drug applications (NDA and ANDA) often do not allow FDA reviewers to gauge the level of product and process understanding supporting a proposed product and manufacturing process design. Therefore, in the current state, regulatory decisions (e.g., setting specifications) have no choice but to utilize a procrustean decision approach which is predominantly based on analytical data obtained from just a few batches (1 bio-batch in the case of ANDA's) used in clinical trials or bioequivalence assessment. To reduce regulatory uncertainty, industry should reduce scientific "uncertainty" through information and knowledge sharing (6).

The FDA has taken the lead to overcome industry concern through a provision for voluntary submission of pharmaceutical development information, coupled with a commitment of support for scientific assessment of this information. This commitment includes among other things: (a) creating opportunities for scientific discussion (early in drug development) between an applicant and FDA review staff, (b) training opportunities for reviewers, (c) recruiting experts in pharmaceutical science and engineering disciplines, (d) developing a quality system that will incorporate the concept of "peer review", and (e) steadily moving towards a question-based quality assessment process. The PAT Guidance and regulatory process have already been established as an example of this general approach, which can be expanded to the entire CMC review process using the ICH Q8 guideline and other tools. The draft ICH Q8 articulated what should be considered as minimal information in a pharmaceutical development report and what could be considered as optional information (3).

In-depth Discussion on Applications of QbD Conceptual Framework

The development of illustrative regulatory applications (examples) of the QbD conceptual framework is an essential next step. Regulatory decision criteria that relates to establishment of specifications on critical quality attributes would be an ideal starting point for further defining QbD. This could be accomplished by outlining key questions that should be addressed in pharmaceutical development studies and illustrating how this information can assist in improving the efficiency and effectiveness of regulatory decisions.

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. Over the past three decades, considerable scientific attention has been given to understanding the mechanism(s) 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. The current scientific understanding and knowledge regarding drug dissolution/release has been predominantly based on studies on oral drug delivery. For non-oral drug delivery systems the principles and methods developed are often generally adopted.

At the end of the 20th Century, we successfully established a comprehensive regulatory decision system for quality assurance and control of drug dissolution or release rate characteristics of solid oral drug products. FDA policy documents currently exist on the topics: (a) drug dissolution/release specifications from solid oral dosage forms and establishment of *in vitro to in vivo* correlations (7, 8), (b) demonstration of drug dissolution/release similarity when formulation and manufacturing changes have to be made (9), and (c) for waiver of *in vivo* bioequivalence studies (10). This was accomplished, in part, due to the dedicated leadership of many FDA staff members, in particular Dr. Vinod Shah. Furthermore, the ICH Q6A guideline on establishing specifications has also been developed (11).

Significant opportunities to build upon the current regulatory decision system and to further improve its effectiveness and efficiency are afforded by: (a) the ability to utilize pharmaceutical development information (e.g., ICH Q8) in regulatory decisions and (b) the availability of new technologies for more effective control of formulation and manufacturing variables that impact drug dissolution process, when combined with a comprehensive systems approach to regulatory quality assessment (e.g., connection CMC review – Clinical Pharmacology &Biopharm review – cGMP inspections).

The development of regulatory decision criteria based on QbD principles for quality assurance and control of drug dissolution or release rate may serve as a model to become a milestone in a journey towards the desired state of pharmaceutical quality in the 21st Century. The QbD approach to drug dissolution specification can lead to discussions on a more effective and efficient means of managing post approval formulation and

manufacturing changes. These principles can then contribute to efficient approaches for establishing therapeutic equivalence of generic drug products.

Framing the Discussion

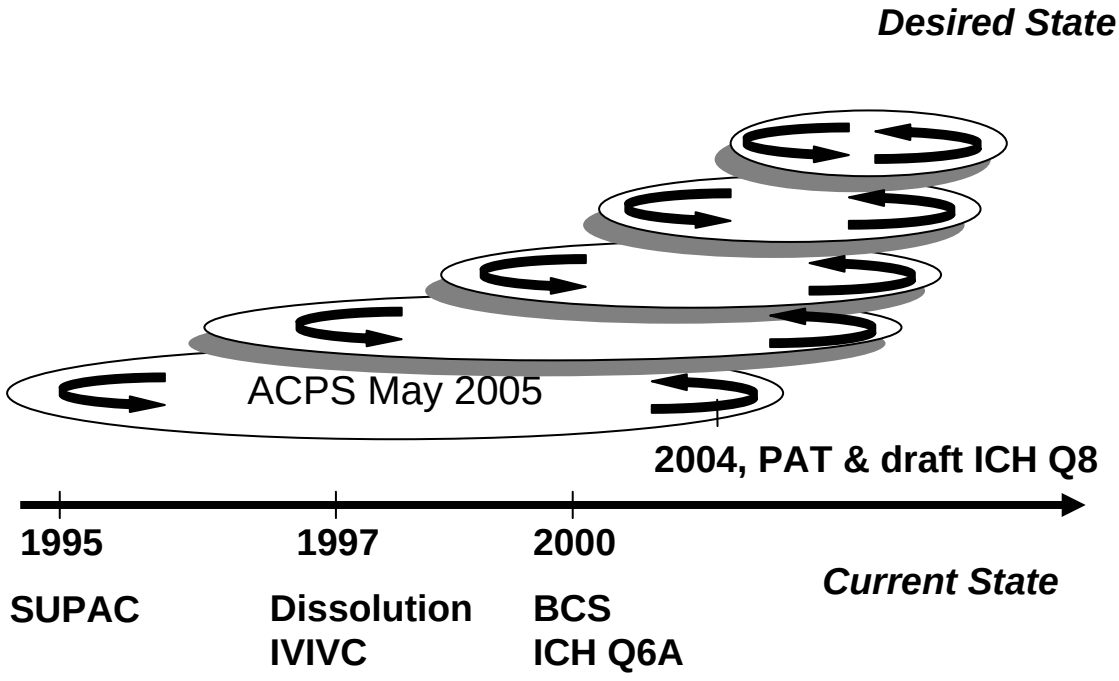
The challenge posed by Dr. Janet Woodcock (Acting Deputy Commissioner for Operations FDA) in her paper entitled "The Concept of Pharmaceutical Quality" (12) essentially frames this discussion. In particular our planned ACPS discussion will seek to address the following three aspects of her challenge.

- *"The scientific challenges facing pharmaceutical manufacturing go well beyond the problem of the clinical readout. Despite the slogan building quality in, most quality assessment today relies on end-product testing. This is a problem in and of itself. In addition, many of the tests methods currently being used have severe limitations in the modern, mass production environment.*
- *"..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."*
- *".. we must turn to the science of manufacturing and the concept of quality-by-design (QbD), which means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches. To achieve QbD objectives, product and process characteristics important to desired performance must be derived from a combination of prior knowledge and experimental assessment during product development. From this knowledge and data, a multivariate model linking product and process measurements and desired attributes may be constructed. Clinical study would then be viewed as confirmatory performance testing of the model."*

The "Desired State" Directional Vector

In the current state, regulatory decisions on quality assurance and control of drug dissolution rate (and many other quality characteristics) are based predominantly on test data from a relatively small test sample size; robust estimates of variance (sample and population) are often not obtained. As a result, the process control strategy and decision criteria essentially reflect compendial standards. Compendial standards are intended to be "market standards" since they have to be applicable to many different manufacturers (i.e., different formulations and manufacturing processes for the same monograph product) and, by definition, are absolute – pass/fail with no room for uncertainty or risk-based decisions (13). Since these are minimal standards (sufficient for ensuring quality fit for intended use of a product), they do not provide an approach to recognize the level of process understanding and control achieved and, therefore, can not facilitate continuous

improvement in efficiency/productivity. Furthermore, for a composite physical functionality such as dissolution, influenced by many physical forces such hydrodynamics, a compendial standard can sometimes be unfair to some manufacturers; apparatus and/or test conditions optimally defined for an originator product can impose constrains on products that follow. In the desired state, where continuous improvement and innovation are facilitated, relationships between in-process controls, final product control limits, and regulatory specifications and/or standards would need to be clearly understood by all stakeholders. An ability to control a product by appropriate measurement tools to a degree higher than minimal standards (minimizes risk of not meeting the minimal standard) should provide both regulatory and technical flexibility for continuous improvement, but only if this improved ability to control is not penalized by narrowing the regulatory acceptance criteria. Tools such as statistical process control can provide a means to evaluate trends so as to prevent deviations due to "special causes" (e.g., under CGMP's). A quality system that reliably ensures this objective can help in justifying regulatory flexibility for continuous improvement. Since a higher degree of process understanding and control (e.g., control of variability) is the critical directional vector towards the "desired state", it may be useful to visualize this vector as the Z-axis of a three dimensional object, the X and Y-axis define the plane (i.e., minimal standards) on which the current state rests. The proposed discussion at the May 2005 ACPS meeting is a re-examination of (inherent assumptions in) current regulatory policies pertaining to quality assurance of drug dissolution rate to find means of improving it and create flexibility for continuous improvement; the relationship of this re-examination to a journey towards the "desired state" may be illustrated as in Figure 1 below.



Discussions at the May 2005 meeting of the ACPS will predominantly focus on physical, chemical, and physiological factors and the dissolution mechanisms underpinning

regulatory decisions. It is recognized that statistical protocols for addressing variability will be an essential component of the regulatory process; however, the statistical discussion should be founded on a strong physico-chemical and clinical pharmacological foundation. Past experience suggests that starting with statistical discussion and/or predominantly focusing regulatory quality discussion on development of statistical methodology can often lead to protracted debates (e.g., the IPAC-RS proposal for a statistical treatment of delivered dose uniformity).

Introduction to Topic #1

The first discussion topic will be on a QbD approach to pharmaceutical quality assurance and control of drug dissolution or release rate characteristics of solid oral drug products. Broadly, this discussion will seek ACPS advice on a regulatory tactical plan for developing a QbD approach to quality assurance of dissolution rate.

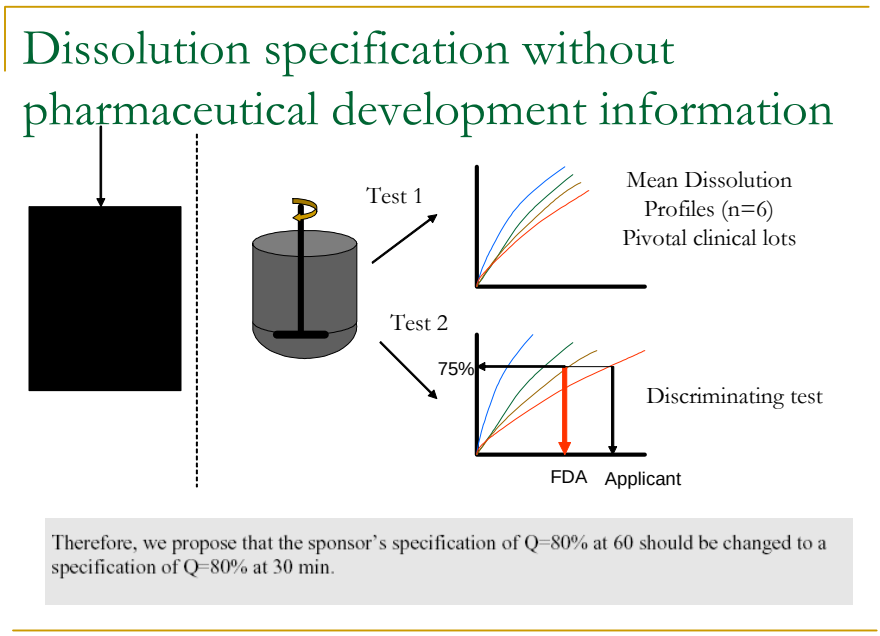
Considerations for Developing a Tactical Plan

The proposed approach for developing a tactical plan is to: (a) outline how structured pharmaceutical development information (pre-formulation material characterization, formulation development and optimization efforts using Design of Experiment, etc.) can provide reliable means for identifying sources of variability and quantifying variability in pivotal clinical materials (the basis for clinical trial data, regulatory clinical risk/benefit assessment and approval decision), and (b) describe why, and how, (contrasting with the current approach) regulatory assessment and utility of such information can facilitate establishment of an optimal target value for dissolution rate and acceptable variability around the target value. The level of quality assurance and control of drug dissolution rate under the proposed approach must be higher than what is achieved under the current system. In addition, it is desirable to seek harmonization with other regulatory authorities (e.g., the "design space" concept in draft ICH Q8), specifically the ICH regions. The higher level of confidence should then be a basis for a flexible regulatory approach (e.g., reducing the need for prior approval supplement process) to facilitate post approval changes that improve productivity and reduce variability (continuous improvement). The key elements of the tactical plan may be categorized into (a) the measurement system, (b) product design and characterization (to include characterization of raw materials, and packaging, stability, and in vivo assessment), and (c) manufacturing process design and its control strategy.

Measurement system capability: In the current state, measurement system variability appears to be controlled by the instrument design specifications and the method suitability criteria that are based on testing standard materials – the calibrator tablets. There are several official dissolution instruments and calibrator tablets listed in the US Pharmacopoeia. Selection of an appropriate instrument for a particular dosage form is, to a large extent, based on experience. The calibrator tablets are essentially manufactured using raw materials and manufacturing technologies similar to other tablet dosage forms; the manufacturing process capability of the calibrator tablet is essentially confounded in its measurement system capability (another dissolution apparatus). Furthermore, the

quality of some calibrator tablets has been a concern for several years, and some of these can exhibit sufficiently large lot-to-lot (and over time within lot) variability to require adjustment of the goal posts (or criteria) for dissolution instrument suitability determination (14, 15). In addition, hydrodynamic variability is also a significant concern that brings into question the applicability of the calibrator tablet approach to different dosage forms designs (16 -21).

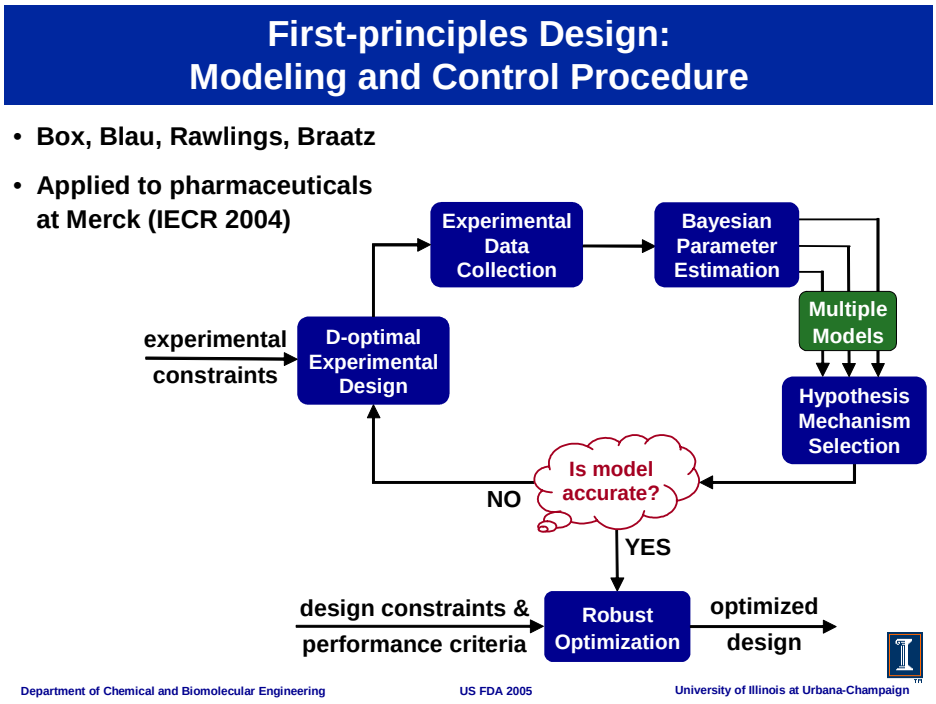
Product Design and Characterization: In the current US regulatory decision system we often only have limited information on dissolution test results. We utilize this information to seek association or correlation with *in vivo* pharmacokinetic data on the same lots. Figure 2 below graphically represents the current approach. The high degree of uncertainty in this decision system is often a source of disagreement and debates between FDA and industry (22, 23).



A structured pharmaceutical development report can provide a means to reduce regulatory concerns and provide a more rigorous scientific framework for decisions on pharmaceutical quality. A structured approach could be empirical (e.g., DOE) or can, in some cases, extend to mechanisms and to first principles. For example, at a recent seminar at FDA, Professor Richard Braatz (University of Illinois, Urbana-Champaign) outlined an approach (see Figure 3 below) that is a good illustration of a structured approach to pharmaceutical development. Such an approach, we believe, can provide a means to achieve the vision articulated by Dr. Woodcock:

- *(QbD), which means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches. To achieve QbD objectives, product and*

process characteristics important to desired performance must be derived from a combination of prior knowledge and experimental assessment during product development. From this knowledge and data, a multivariate model linking product and process measurements and desired attributes may be constructed. Clinical study would then be viewed as confirmatory performance testing of the model."



The essential elements of pharmaceutical development information with respect to drug dissolution rate may include:

Drug substance characteristics: Characterization of solubility, stability (including mechanism of degradation), ionization, permeability (including mechanism of absorption) and information on control strategy for polymorphic form, particle size, moisture content and impurities. Although much of this information is currently scattered in regulatory applications, it is anticipated that the pharmaceutical development section will identify interrelationships among these characteristics and dissolution rate with an emphasis on which of these are critical.

Raw materials (excipient) selection criteria could include compatibility justification, intended function in a formulation and characteristics important for these functions, and justification of the adequacy of the proposed control strategy. Utility of prior knowledge will be useful, especially with respect to sources of variability (from manufacturing) and how this knowledge may support proposed control strategy. Furthermore, development information specifically targeted to demonstrate the adequacy of the proposed control strategy will provide a comprehensive view to the regulators.

Product design considerations may include anticipated or desired dissolution mechanism and critical factors based on prior knowledge and how this information guides product

development. Physical and chemical stability considerations, potential failure modes, and packaging considerations are an integral part of design considerations. Screening strategy for experimental product designs, specifically the choice of an initial dissolution test method for formulation screening and how and why this method was justified based on drug characteristics and product design considerations, would be useful to establish a link between the pharmaceutical development knowledge and characterization of the pivotal clinical product and thereby support establishment of an acceptable variability benchmark. As the development process proceeds, what were the scientific considerations for (a) *in vivo* drug dissolution/release evaluation and (b) to confirm and/or support postulated *in vivo* performance (e.g., relative bioavailability, etc.)? A strategic approach can provide a means to demonstrate/evaluate clinical relevance of a proposed *in vitro* characterization of clinical trial products and the proposed control strategy. Pre-formulation and pre-clinical (e.g., studies in animal models) characterization may provide additional supporting knowledge.

Regulatory assessment of pharmaceutical development information should focus on knowledge/information summarized in the pharmaceutical development section. To simplify the assessment process and to ensure sound decisions regarding adequacy of a proposed control strategy (for the pivotal clinical trial products or bio-batch), demonstration of an ability to reliably predict (a priori) quality/performance of experimental and proposed clinical trial product or bio-batch would be desirable. This ability can be further supported by sound scientific explanation, based on prior development information, and the observed performance of products (e.g., characterizing studies, stability evaluation, and pharmacokinetic evaluation) in various clinical phases.

Manufacturing process design and its control strategy: Initial product design considerations, along with a structured approach to process design, should consider potential product failure modes (chemical and physical) in developing the process control strategy. Key questions to be addressed may include: How does a selected manufacturing process (1) minimize the risk posed by product failure modes identified (or inherent in its design) and (2) account for and control variability in the raw materials and variability induced (in material attributes that relate to quality attributes, e.g., dissolution) likely to be introduced (likelihood may be derived from prior knowledge) by the process itself? The failure modes and risk factors often may be ascertained based on mechanisms of drug dissolution/release and drug degradation. Characterization of the clinical trial product can generally provide a means to evaluate the reliability of a proposed manufacturing process to deliver the intended product design specifications.

Specific tactical steps include:

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. Note that the external calibrator tablet approach is not currently utilized in the EU and Japan. In this regard, the Japanese perspective on dissolution testing (24) addresses variability due to vibration in dissolution instruments (25).

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 (1) characterize reproducibility and repeatability (e.g., DOE based Gauge R&R for destructive samples) of the measurement system and (2) 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.
    a. An ability to define and benchmark acceptable variability in the pivotal clinical trial product is important to define appropriate dissolution rate specification (acceptance criteria or tolerance limits). Certain challenges in the current approach for establishing acceptance criteria have been discussed by Japanese regulators (24) and others (22).
    b. Furthermore, with the current confounding of calibrator variability, measurement system variability poses other significant challenges. For example, the method suitability criteria based on the USP 10-mg Prednisone Calibrator tablet (Lot O0C056) can be as wide as 27 – 48 % of dissolution from the calibrator, whereas the regulatory decision criteria for two products (e.g., pre- and post approval manufacturing change) to be considered similar, limits the allowable mean difference to about 10 %.
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.

References – Topic #1

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Introduction – Topic #2

Approval of a new drug application (NDA) establishes the intended use (label) of a product based on an assessment of acceptable risk-to-benefit ratio. Approval of an ANDA establishes *therapeutic equivalence* of a generic product to deliver the intended use and equivalent risk-to-benefit ratio for the reference NDA product. The decision of *therapeutic equivalence* entails the decision of equivalent quality, and a similar decision criterion is used for managing post approval product and manufacturing changes for both generic and innovator products. These decision criteria may be summarized as follows (the Orange Book):

> *Drug products are considered to be* ***therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.*** *FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.*
>
> *Generic products may differ in certain other characteristics such as shape, scoring configuration, drug release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time and minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage conditions. When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.*

A generic drug product intended for systemic absorption by the oral route of administration is considered to be pharmaceutical equivalent to a reference product only if it contains the same (chemical) active, in identical amount, and in the same dosage form (e.g., tablet and capsule). The generic product can differ from its reference product in several aspects such as its composition (e.g., excipients), design features such as drug release mechanism, and manufacturing process. *In vivo* bioequivalence demonstration is necessary for oral drug products that present "a known or potential bio -problem" (criteria based on prior knowledge and characteristics such as aqueous solubility, intestinal permeability, etc.). Bioequivalence studies are conducted in normal healthy volunteers using a cross-over design and are intended to demonstrate that the 90% Confidence

Interval for generic/innovator ratio of key pharmacokinetic parameters (e.g., C_{max} and AUC) are within 80-125% (acceptance goal post). This same acceptance criteria generally applies for all oral dosage forms (i.e., a procrustean standard) and is considered to cover "worst case" scenarios. Since this decision process relies on prior knowledge and limited (analytical) data/information on a specific product, it essentially is an "***uncertainty management***" process. Its efficiency then is significantly dependent on the availability of "generalize-able" knowledge. In terms of quality standards, compendial monographs on drug substance and drug product serve this role and their construction can have significant impact on regulatory decisions (with respect to allowable differences in generic products). These standards, standard test methods (e.g., dissolution test) and the bioequivalence criteria then define an ***acceptable level of variability***. Achieving and conforming to these standards is then the characteristics of a generic drug quality decision system for achieving its goal - approved generic product is *expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.* Post approval reports on potential in-equivalence observations are then monitored.

Table 1: Goal and Characteristics of the Pharmaceutical Quality Decision System for generic products (e.g., systemic delivery via the oral route of administration)

<table>
<tr><td colspan="4">Goal: approved generic product is expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling</td></tr>
<tr><td>Characteristics</td><td>Uncertainty</td><td>Variability</td><td>Risk</td></tr>
<tr><td>Pharmaceutical Equivalent</td><td>Same active, identical amount, same dosage form, and route of administration. Identity, Strength Quality, Purity.</td><td>Compendial or other standards</td><td rowspan="5">Prior Knowledge (NDA)

Post Approval:

Monitoring program

Such as MedWatch

Consumer Complaints

Therapeutic Inequivalence Coordinating Committee</td></tr>
<tr><td rowspan="2">Need for Bioequivalence Assessment</td><td>Do not present a known or potential bioequivalence problem. Acceptable in vitro standard</td><td>Compendial Dissolution test method</td></tr>
<tr><td>Present a known or potential bio -problem. Appropriate bioequivalence standard</td><td>90% Confidence Interval of Test/Ref ratio for rate and extent of absorption in 80 -125% range</td></tr>
<tr><td>Adequately Labeled</td><td>Similarity with reference label, medication errors.,,</td><td>Certain differences due to changes in the manufacturer, distributor, pending exclusivity issues, or other characteristics</td></tr>
<tr><td>Manufactured in conformance to CGMP's</td><td>Process Validation and Quality System</td><td>Deviations, Out of Specifications,...</td></tr>
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A QbD approach via pharmaceutical development information can potentially provide an excellent means to address a number of challenges previously discussed at ACPS meetings without complete or satisfactory resolution – for example: bioequivalence of highly variable drugs, bio-in-equivalence criteria, pharmaceutical and therapeutic equivalence of locally acting drug products (e.g., topical drug products). In addition, further elaboration and extended application of the Biopharmaceutics Classifications System(BCS)-based waiver of *in vivo* bioequivalence is essentially an extension of Topic #1 discussions.

At the May 2005 meeting of the ACPS we plan to initiate discussions on how pharmaceutical development information may facilitate regulatory decisions on approval of generic drug products. For this initial discussion, we will briefly outline our thoughts on three topics:

1. How can pharmaceutical development information help to extend the applications of BCS-based waiver of *in vivo* studies for immediate release products?
    a. Backgound – BCS Workshop Report
2. How can pharmaceutical development information be utilized to address the challenge of highly variable drugs?
    a. This topic was previously introduced at the April 2004 meeting of the ACPS http://www.fda.gov/ohrms/dockets/ac/04/briefing/4034b1.htm
3. Establishing therapeutic equivalence of topical products
    a. Robert Lionberger's presentation at the April 2004 ACPS meeting (Topical Bioequivalence Update)