Food and Drug Administration

Meeting of the

Pharmaceutical Science

and

Clinical Pharmacology

Advisory Committee

September 20, 2018 Briefing Information

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Food and Drug Administration

Meeting of the Pharmaceutical Science and Clinical Pharmacology (PSCP) Advisory Committee

September 20, 2018

BRIEFING INFORMATION

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MEMORANDUM

TO: Members, PSCP

FROM: Michael Kopcha, Ph.D., R.Ph.
Director, Office of Pharmaceutical Quality/CDER/FDA

DATE: August 23, 2018

RE: PSCP Meeting September 20, 2018

Dear Committee Members and Invited Guests,

We look forward to your participation in the Pharmaceutical Science and Clinical Pharmacology Advisory Committee (PSCP) meeting on September 20, 2018.

This Advisory Committee focuses on important science issues being considered and/or addressed in the Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER). As you know, this office is mainly focused on the assessment of the quality of pharmaceutical products. Through your participation and advice on the advisory committee, we develop and finalize our standards for assessing and approving products and setting policy for regulatory decision-making.

This specific meeting will focus on two topics related to OPQ's priority of promoting the availability of better medicine. During the morning session, the committee will discuss the modernization of assessing drug applications through a Knowledge-aided Assessment and Structured Application (KASA) initiative. FDA will seek input on the potential enhancement of submission format consistent with KASA to improve the efficiency and consistency of regulatory quality assessment. During the afternoon session, the committee will discuss advances in dissolution testing, mechanistic physiologically-based pharmacokinetic (PBPK) modeling and in vitro-in vivo relationships (IVIVR). FDA will seek input on establishing patient-focused dissolution standards for extended-release solid oral drug products. Background materials for each of the topics are attached.

We look forward to a very productive meeting in September. We value the opportunity to solicit your assistance in defining and solidifying OPQ's direction in developing sound, scientific responses to emerging issues.

At the start of the meeting on September 20th, I will outline the goals and objectives for our meeting and I will also update you on ongoing OPQ initiatives and activities.

Topic 1 – Knowledge-aided Assessment and Structured Application (KASA)

Timely development, assessment, and approval of safe and effective drugs is pivotal for assuring the American public has access to quality medicines. At present, the new drug and generic quality assessment is performed using a written narrative. To modernize the assessment of drug applications, a KASA system has been initiated. KASA could become a system that captures and manages information about a drug product including risk identification, mitigation and communication, and control strategy. It does this through a structured IT framework that could completely replace the current unstructured text-based, narrative assessment. During the morning session, the committee will discuss approaches of a KASA system for quality submission and assessment.

Draft Discussion Points for the Committee:

Relating to the KASA initiative, should the FDA consider the enhancement of submission format to improve the efficiency and consistency of regulatory quality assessment?

Topic 2 – Patient Focused Quality Standards for Extended-Release Solid Oral Drug Products; In Vitro and In Vivo Relationships (ER IVIVR)

Since its development in the late 1950s and its acceptance by the United States Pharmacopeia (USP) Convention in the 1970s, in vitro dissolution testing has been widely used as a quality control tool for solid oral dosage forms. More recently, it has evolved into an invaluable tool to forecast in vivo performance of drug products. In the context of extended-release solid oral dosage forms, dissolution is critical in connecting product quality to in vivo performance through in vitro-in vivo correlation (IVIVC). More recently, this connection has been made through mechanistic physiologically-based pharmacokinetic (PBPK) modeling and simulation leading to in vitro-in vivo relationships (IVIVRs) and patient-focused quality standards. During the afternoon session, the committee will discuss dissolution and IVIVR approaches relating to patient-focused quality standards for extended-release solid oral drug products.

Draft Discussion Points for the Committee:

Should the FDA establish patient-focused dissolution standards for extended-release solid oral dosage forms?

We are looking forward to a very stimulating discussion with the committee on the selected topics. Have a safe and enjoyable journey to Silver Spring, MD. The meeting will be held at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Room 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002.

September 20, 2018

Topic 1

KASA

Background Information for the FDA Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee

September 20, 2018

Topic 1: KASA
Knowledge-aided Assessment & Structured Application (KASA):
A New Approach that Modernizes FDA's Quality Assessment of Regulatory Drug Applications

I. Introduction

Timely development, assessment, and approval of safe and effective drugs is pivotal for assuring the American public has access to quality medicines. The Office of Pharmaceutical Quality (OPQ) focuses on the *quality* of drugs, which serves as the foundation for the established parameters of safety and efficacy. OPQ is responsible for the quality assessment of nearly every type of human drug marketing application including New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Biologics License Applications (BLAs), including 351(k) applications (i.e., biosimilars). OPQ also performs the quality assessment of Investigational New Drug Applications (INDs) and establishes quality standards for over-the-counter drug products and facilities. At present, the OPQ quality assessment is a written narrative, which results in dense, lengthy documents. In other words, this is a 20th Century approach meant for a time when most regulatory submissions were submitted on paper. OPQ recognizes the need for modernizing the current assessment approach and is in the process of creating a new system named Knowledge-aided Assessment & Structured Applications (KASA), as shown in Figure 1.

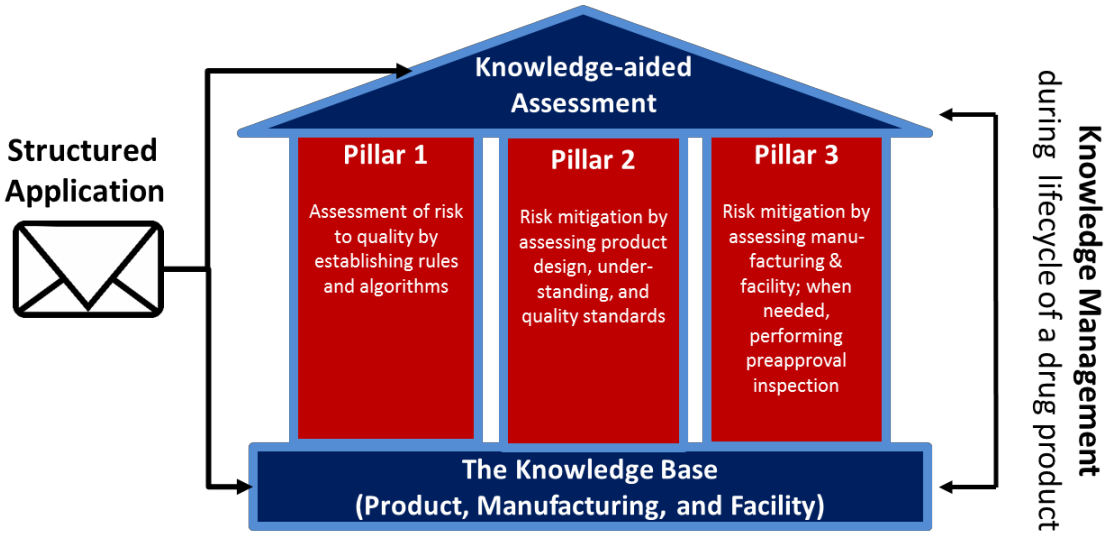

Figure 1. Knowledge-aided Assessment & Structured Application (KASA) system

The KASA system is designed to:

- Capture and manage knowledge - such as established conditions - during the lifecycle of a drug product;
- Establish algorithms for risk identification, mitigation, and communication;
- Perform computer-aided analyses of applications to compare regulatory standards and quality risks across approved applications and facilities; and
- Provide a structured assessment that radically eliminates text-based narratives and summarization of provided information

The KASA system will promote issue-based quality assessment using structured data and information to improve the efficiency, consistency, and objectivity of regulatory actions. This advisory committee meeting will describe factors that prompted the development of the KASA system, the vision for KASA, and the benefits it could provide upon implementation. The meeting will seek input on the format and content of regulatory applications.

II. Current State and Why KASA is Needed

The Agency recognizes the need for internal change in response to increasing expectations from the pharmaceutical industry, public demands, and technological advancements to keep pace in the 21st Century. With the reauthorization of the Prescription Drug User Fee Act (PDUFA VI), Biosimilar User Fee Amendments (BsUFA II), and Generic Drug User Fee Amendments (GDUFA II), OPQ has experienced a large volume of regulatory drug applications along with, in some cases, shorter assessment timelines. Apart from the workload, OPQ faces challenges related to the quality assessment itself, which is still a freestyle text narrative and summarization of information submitted by applicants. This assessment model poses barriers toward best practices for managing quality, lifecycle knowledge sharing, and overall modernization.

Currently, written assessments consist of unstructured text and often have excessive summaries of application data, including tables and other information "copied and pasted" from the actual application. Thus, key elements of the quality assessment such as risk assessments and evaluation of mitigation approaches are often not readily identifiable in these lengthy documents. This results in cumbersome knowledge management and inefficient communications. In addition, assessments rely heavily on the knowledge and expertise of the assessor, which can potentially lead to inconsistencies in assessment. While assessor expertise is highly valued in OPQ, the current approach is hindered by the absence of databases to capture current knowledge that would aide in accessing critical information and making more objective decisions. Coupled with insufficient knowledge management tools, this unstructured text approach can result in inconsistencies and difficulties when comparing products.

The lengthy unstructured text narrative with dispersed information and the lack of efficient knowledge management make it difficult for OPQ to compare relative quality and relative risk across drug products and facilities. This makes it difficult to capture the 'state of quality' for a

product at any given time. This becomes especially evident when assessing residual risks with post-marketing quality changes during the drug product lifecycle. These challenges may lead to late interventions in preventing or addressing drug shortages or quality failures of marketed drugs. To meet the above challenges, OPQ is developing the KASA system to modernize the quality assessment of drug applications to include structured information. This promotes consistency and enables a much-needed knowledge management tool that improves efficiency and the overall quality assessment process.

III. More About KASA – The What

KASA is a system that captures and manages information about intrinsic risk and mitigation approaches for product design, manufacturing, and facilities, in a structured template. This is intended to facilitate a concise and consistent quality assessment and largely replace freestyle text. The KASA interface tabulates the following for each critical product quality attribute:

1) Inherent risk to quality
2) Mitigation approaches - using a list of generalized structured descriptors related to pharmaceutical design, development, control strategy, and facility implementation
3) A concise summary from the assessor detailing how the generalized approaches are applied in the regulatory application
4) Links to supporting information from the application.

The house depicted above in Figure 1 represents KASA. The knowledge base represents the house's foundation and encompasses the historical information about the drug product and its manufacturing available to the Agency. Above the foundation are pillars that provide structure and a framework. Each pillar represents a different phase of KASA's development. The following Sections A through C provide details about each pillar of the house, representing noteworthy aspects of development. Section D discusses the long-term vision for structured applications which would greatly enhance the value and significance of the KASA by automating uptake of data into the system.

A. Pillar 1: Assessment of Risk to Quality by Establishing Rules and Algorithms

KASA establishes within its user interface predefined rules and algorithms to estimate the initial inherent product and manufacturing risks. After the assessor enters information in the system based on the application, a failure modes, effects and criticality analysis (FMECA) approach is employed. This is used to objectively and quantitatively assess and rank risks associated with the failure modes of drug product design and manufacturing. These are the risks that have the greatest chance of causing product failure or unexpected harm to the patient. Product risk considers each critical drug product quality attribute (such as assay/potency, purity, uniformity, dissolution, etc). Manufacturing risk considers the impact of the proposed material transformation steps on the product quality attributes, and the potential risks involved with implementing the proposed control strategy at the manufacturing site.

B. Pillar 2: Risk Mitigation by Assessing Product Design and Understanding, and Quality Standards

The inherent risk identified in Pillar 1 is mitigated by design of the product and the use of patient-focused quality standards. Product risk mitigation focuses on the drug substance characteristics and drug product design, understanding, and control. Drug substance characteristics considered when assessing risk include therapeutic index, complexity of manufacturing, and adequacy of control of the identity, purity, stability, and quality. Product risk assessment includes the product design, intended use, degree of product understanding, and product quality control inherent to the critical quality attributes (CQAs).

Drug product design determines whether the product is fit for intended use, can meet patients' needs, and maintains its performance through its proposed shelf life. Product understanding is the ability to link input critical material attributes (CMAs) to output CQAs so that input material attributes (e.g., drug substance, excipient, in-process material, primary packaging material) can be appropriately controlled to mitigate risks to the product quality. Within the KASA system, this type of product understanding is captured using drop-down menus with structured descriptors that objectively describe these aspects of product understanding and control strategy. The knowledge captured with such a system enables mitigation of product risk to be compared across applications and facilities.

Pillar 2 also includes the assessment of the applicants' specifications and acceptance criteria to determine their acceptability as a part of established conditions. By establishing acceptance criteria based on desired clinical performance, instead of process capability or manufacturing process control, it increases flexibility within the pharmaceutical manufacturing sector while continuing to maintain quality.

C. Pillar 3: Risk Mitigation by Assessing Manufacturing and Facility, and Performing Approval Inspections

Manufacturing risk mitigation focuses on design and implementation of the manufacturing process. A manufacturing process is generally considered well understood and controlled when:

1) All critical sources of common cause variability are identified and explained
2) Variability is managed by the process at all scales through successful implementation of the control strategy
3) Process performance and product quality attributes can be adequately and reliably monitored and controlled

Facility risk mitigation, or the implementation element of manufacturing risk, focuses on the manufacturer's GMP status and ability to support the control and continued performance of the operations. Determination of risk mitigation leverages the demonstrated capabilities of the manufacturing or testing facilities as it relates to the proposed manufacturing process. It includes evaluation of the facility's recent manufacturing history, knowledge of the facility with the unit operations included in the

application, and relevant quality signals for any similar marketed products, including applicable Field Alert Reports (FARs), any associated recalls, regulatory/advisory actions, and available foreign regulatory agency reports.

After evaluating development information, the proposed control strategy, and the firm's known capabilities, there may still be significant risk concerning the ability of the applicant to successfully produce the quality product. This remaining risk can be further assessed by performing a pre-approval inspection (PAI) or post-approval inspection (PoAI). The PAI/PoAI assesses whether the facilities named in the manufacturing section of an application can perform and adequately control the proposed operation(s) in conformance to CGMP requirements. Additionally, a PAI evaluates whether the data submitted in the application are reliable, accurate, and complete. Under KASA, manufacturing process design and implementation risks are evaluated and captured using pre-defined descriptors that objectively capture aspects related to manufacturing and facility understanding and control so that objective standards are used to identify the need for PAIs.

D. Structured Application

Looking toward the future, knowledge-aided assessment would be greatly enhanced if applicants submit applications more streamlined in layout with structured data that integrates with the assessment system. Regulatory drug applications are currently submitted to FDA in the electronic common technical document (eCTD) format. Despite some benefits, the eCTD poses challenges for FDA assessors because the submitted content does not follow the development flow, contains unstructured data, and varies in the level of granularity provided. Furthermore, the documents are in pdf format so information cannot be easily searched/mined, making lifecycle management challenging.

Although KASA is being primarily developed as an assessment tool, it is capable of alleviating problems associated with electronic regulatory drug applications. In the future, it is conceivable that submission structure recommendations will be made to better interface with KASA's structured assessment approach. This would allow applicants to succinctly and consistently summarize steps taken to mitigate inherent risks via development studies, control strategies, and local CGMP facility controls. Under this paradigm, automated tools would be used to populate the KASA template from the structured submission with, for example, specifications and critical process parameter ranges. This would eliminate administrative tasks for the assessor and improve the assessment efficiency by allowing assessors to focus on high risk areas. This longer-term goal would be a significant step towards modernizing and bringing the overall quality assessment process into the 21st Century.

IV. Benefits Offered by KASA

The KASA system moves regulatory application assessment from the current unstructured text document to an issue-based regulatory and technical assessment using structured data and information with standard formatting, a common vocabulary, and a uniform output. In turn, this improves consistency, transparency, communication, and objectivity of regulatory actions as

well as knowledge management within the Agency.

KASA, with access to structured knowledge, will have tools that enable assessors to automatically retrieve historical data and facility information to better inform the regulatory evaluation and decision-making process. KASA will facilitate the assessment of risk using rules and algorithms, which in turn reduces subjectivity of documentation and the time burden. Furthermore, prior to assessment, submitted applications will be checked against KASA informatics to detect any outliers in control strategy and risk attributes as compared to the broader KASA database. The built-in rules and algorithms together with the detection of outliers allow assessors to focus on high-risk areas and issues. This improves the quality and efficiency of the regulatory assessment by semi-automating FDA's quality assessment. Ultimately, this facilitates the introduction of breakthrough therapeutics and low cost, high-quality generic drugs to meet medical needs.

Finally, by evaluating risks and mitigation steps, KASA captures and conveys residual product, manufacturing, and facility risk for each regulatory submission. It will also be instrumental in capturing established conditions. Succinctly identifying the main mitigating factors and residual risk aids the Agency's assessment of post-approval changes and the lifecycle management of drug products. This can help focus post-approval and surveillance inspection resources on the riskiest products or those for which on-site controls are essential for ensuring critical quality attributes. In this way, the FDA achieves more efficient regulatory oversight by appropriately focusing resources on the high-risk products.

V. Conclusions

KASA is a new system intended to modernize the quality assessment of regulatory drug applications. KASA represents a concept shift from the outdated assessment practices of the past, to a new, more efficient way of handling information and resources. When fully developed and implemented, KASA will contribute to:

1. assuring patient focused quality standards and the objectivity of regulatory actions through knowledge management;
2. enhancing science- and risk-based regulatory approaches through established algorithms; and
3. enriching regulatory oversight through lifecycle management of products and facilities

Ultimately the KASA system advances OPQ's focus on pharmaceutical *quality*, the foundation for ensuring the safety and efficacy of drugs. It takes the Agency's *quality oversight* to the next level through modernization.

Draft Discussion Points for the Committee

Relating to the KASA initiative, should the FDA consider the enhancement of submission format to improve the efficiency and consistency of regulatory quality assessment?

September 20, 2018

Topic 2

ER IVIVR

Background Information for the FDA Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee

September 20, 2018

Topic 2: ER IVIVR

Patient-Focused Quality Standards for Extended-Release Solid Oral Drug Products: In Vitro and In Vivo Relationships

Introduction

A patient-focused quality standard is a criterion to which a drug product should conform to deliver the intended therapeutic benefit. Establishing such standards can help to not only reject batches with poor quality, but also to increase flexibility in pharmaceutical manufacturing by eliminating any relationship between standards and process capability. Patient-focused quality standards lead us toward fulfilling the FDA's vision of "a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight" [1].

To support patient-focused quality standards, it is important to develop methodologies that can accurately characterize in vivo systemic exposure from in vitro drug product characterization. In this respect, dissolution testing is a critical tool, as it is the main in vitro test that probes the extent and rate of in vivo drug product release. For extended-release solid oral drug products an in vitro dissolution provides information on in vivo drug product performance which can used to predict drug in vivo performance, provided an in vitro and in vivo relationships (IVIVR) is established. However, developing a biopredictive dissolution test that can predict in vivo PK profile from in vitro dissolution test via IVIVR can be challenging.

This advisory committee meeting will cover recent developments in regulatory dissolution testing, predictive dissolution testing, and the advances in and physiologically-based pharmacokinetic (PBPK) modeling to facilitate the development of biopredictive dissolution testing. The meeting will also include discussion of the current and future states of regulatory expectations for dissolution testing for ER solid oral drug products.

Recent Progress in Regulatory Dissolution Testing Criteria

At the 2012 FDA Advisory Committee for Pharmaceutical Science meeting, the committee discussed the use and limitations of in vitro dissolution testing and encouraged the research of modeling and simulation to better understand relationships between in vitro dissolution and in vivo performance. Based on the mechanistic understanding of the in vivo dissolution of highly soluble drugs, FDA recently issued a guidance entitled "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances" [2].

The guidance provides recommendations on standard dissolution methodology and specification criteria that are appropriate for immediate release solid oral dosage forms that contain high solubility drug substances. In this manner, even in the absence of an apparent IVIVR, patient-focused dissolution standards can be proposed based on: (1) the knowledge of key characteristics of drug substance and drug product that govern the in vivo absorption and (2) the knowledge of the interplay of those factors. The guidance recommends that the drug product dissolution criterion be established based on high solubility with the following recommendations: "The drug product dissolution acceptance criterion is based on the high solubility of the drug substance. If an alternate acceptance criterion is proposed, the sponsor/applicant should provide additional data to support the proposed acceptance criterion. Additional supportive information could include appropriate in silico modeling in addition to dissolution performance data. For immediate-release solid oral drug products containing a high solubility drug substance (as defined herein), the dissolution criterion is Q=80% in 30 minutes."

Current State of Dissolution Testing Criteria for Extended-Release Oral Dosage Forms

In 1997, FDA issued guidance consistent with the theme of patient-focused dissolution standards: "Extended Release Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In Vivo Correlations" Guidance for Industry [3]. In general, the setting of dissolution criteria is based on the dissolution data from pivotal clinical batches using multiple-time-point criteria that cover the entire profile of drug release. Selection of the acceptance ranges is based on mean target value ±10% and not less than 80% for the last time-point. Wider ranges could be acceptable provided adequate justification is given (e.g., supported by an approved IVIVC model).

There are three categories of IVIVC models (level A, B, and C correlations) included in the guidance. Level A IVIVCs represent a point-to-point relationship between in vitro dissolution and the in vivo input rate of the drug from the dosage form. They are the most frequently used for regulatory submissions since they are most informative. A Level A IVIVC aims to establish a link between the full in vitro dissolution profile and the full in vivo absorption profile. This IVIVC confirms the predictive capability of an in vitro dissolution test towards in vivo PK performance. Therefore, it can be used to justify dissolution acceptance criteria and support manufacturing changes.

A Level B IVIVC uses the principles of statistical moment analysis to correlate parameters derived from in vitro dissolution profile (e.g. mean dissolution time), with those from in vivo profiles (e.g., mean residence or absorption time). A Level C IVIVC aims to establish a single point relationship between a dissolution parameter (e.g., % of drug dissolved at a given time) to one of the mean PK parameters (e.g., AUC, Cmax or Tmax). Both Level B and Level C IVIVCs do not represent the actual in vivo plasma level curves and are unable to predict the complete in vivo PK profiles. This limits their application in regulatory scenarios. However, a Multiple-Level C IVIVC which relates one or several PK parameters of interest to the amount of drug dissolved at several time points of the dissolution profile, can be as useful as a Level A IVIVC. This is the case when both AUC and Cmax are considered in the correlation to percentage dissolved at multiple representative time points covering the entire dissolution profile(s).

Since the issuing of this FDA guidance in 1997, few regulatory applications have used a Level A or a Multiple-Level C IVIVC to establish in vitro dissolution criteria. This is likely attributed to scientific challenges in developing a Level A or Multiple-Level C IVIVC as well as insufficient attention and investment. However, the lack of predictive in vitro dissolution poses a significant risk to patients for extended-release solid oral drug products, as it prevents the establishment of true patient-focused quality standards. As an example, the withdrawal of Budeprion XL can be associated with the lack of clinical relevance of the quality control dissolution test [5].

Advances in Predictive Dissolution Testing

Compendial dissolution methods based on U.S. Pharmacopeia (USP) are relatively simplified models with limited or no consideration of the in vivo dissolution dynamics of the GI tract. To evaluate and forecast how an extended-release solid drug product would perform in vivo, attention has been paid to the development of biorelevant dissolution models mimicking in vivo conditions [5]. These innovations include the use of (1) biorelevant media (e.g., simulated fluid in the fasted or fed stomach, small intestine, and colon); (2) novel test equipment such as USP Apparatus 3 (BioDis®) and Apparatus 4 (Flow though cell) or other customized equipment to simulate the changing GI environment; (3) complex test system to simulate the dynamic physiological processes within the GI tract such as multicompartimental dissolution models, artificial digestive system etc. [6]. However, the overall utility of such approaches in terms of feasibility of use (validation, analytical support, etc.) in quality control environments and general utility throughout the regulated industry (cost, reproducibility, etc.) has not yet been realized. Moreover, as these innovations in dissolution testing were rarely seen in the regulatory submission, the significance of these innovation to improve dissolution testing in term of biopredictive capability is unclear and deserves further evaluation. .

In 2014, the FDA funded a research program to investigate: (1) in vivo studies in humans to further improve the understanding of the intraluminal processing of oral dosage forms and dissolved drug along the GI tract, (2) advancement of in vitro methodologies that incorporate higher levels of in vivo relevance, and (3) computational experiments to study the local processes underlying dissolution, transport, and absorption within the intestines. The outcome of these studies may reduce and simplify oral drug product testing while significantly reducing the regulatory burden to the pharmaceutical industry [7]. A current FDA study on biorelevant predictive dissolution seeks to identify and understand the impact of critical quality attributes on in vivo performance [8]. The study developed a non-compendial dissolution method to simulate contractile forces along the Gl tract during dissolution testing. In addition to this method, there are many other in vitro models described in the literature [9]. Examples of these systems are the TNO TIM–1 system and the dynamic gastric model (DGM) and Gastro intestinal Simulator. The value and utility of these new models are being evaluated.

Evolution of Physiologically-based Pharmacokinetic Modeling

With the advancement of computational technology, modeling and simulation has become an indispensable tool in various stages of drug development and regulatory approval. The development of physiologically-based pharmacokinetic (PBPK) models incorporated with mechanistic absorption platforms has significantly enhanced the ability to predict oral absorption

and the in vivo PK of a drug product. In the past several decades, PBPK absorption models have advanced from the early compartmental absorption and transit (CAT) model [10] to a now much more sophisticated platform that captures more physiological complexities of the gastrointestinal (GI) tract [11]. PBPK absorption modeling can integrate physicochemical properties of drug substance, formulation characteristics of drug product, and system physiological parameters. In doing so, it can delineate the complex mechanisms governing drug absorption, distribution, and elimination. This can provide a more accurate prediction of the impact of manufacturing and formulation on drug in vivo PK profiles.

Drug release plays a critical role in defining bioavailability for an extended-release solid oral drug product. In vitro dissolution is often the critical parameter in a PBPK absorption model to predict drug systemic exposure. In return, PBPK modeling can help in developing a predictive in vitro dissolution test. Under the mechanistic framework provided by a PBPK model, the in vivo drug dissolution profile in the GI tract can be deconvoluted from GI transit, drug permeation, gut wall metabolism or first-pass metabolism, and drug disposition. This provides more realistic information for adjusting the in vitro testing conditions to mimic in vivo drug dissolution. As such, the likelihood for a successful IVIVR is highly increased, and the predictive capability of an in vitro dissolution test may be achieved. This modeling approach adds a patient focus to the establishment of in vitro dissolution criteria. It can ensure that all lots meeting these criteria will maintain the desired in vivo performance.

Future State of Dissolution Testing for Extended-Release Oral Drug Products

To promote patient-focused drug product quality, there is a critical need to develop predictive dissolution tests to be used as effective surrogates to establish the clinical relevance of quality standards. The in vivo performance of an extended-release oral drug product is determined by the interplay of various physiological and dosage-form derived parameters. Dissolution method development should be based on the comprehensive understanding of physicochemical properties of the drug substance, the release mechanism of the formulation, and the biological environment in which the product will be exposed in patients. Using biorelevant testing conditions in the attempt to resemble the conditions of in vivo dissolution can be the first step to understanding formulation release characteristics. Employing an in silico modeling approach (e.g., PBPK absorption modeling) provides insight into in vivo drug dissolution, taking into account the interplay of drug product physicochemical properties with the GI physiological environment. Different dissolution testing methodologies and conditions might be explored to find an optimal test that relates to in vivo conditions. Combination of the innovations in dissolution methodology with in silico approach is encouraged to facilitate biopredictive method development. The development of biopredictive dissolution test as well as IVIVR is recommended to be planned along with drug development process and be evaluated by clinical PK studies throughout product development program.

The desired future state of in vitro dissolution testing for extended-release solid oral drug products is an in vitro dissolution test that provides predictive insight to in vivo performance. This ensures high quality drug products that maintain safety and efficacy throughout the product lifecycle. With an IVIVR, the impact of critical material attributes and critical process parameters on in vivo performance can be quantitatively assessed by in vitro dissolution. This provides scientific and risk-based knowledge to support patient-focused quality standards.

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Draft Discussion Points for the Committee

Should FDA establish patient-focused dissolution standards for extended-release solid oral products?

Background Information for the FDA Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee

September 20, 2018

Topic 2: ER IVIVR REFERENCES AND SUPPORTING DOCUMENTATION

Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2018
Biopharmaceutics

1074043 FNL
08/01/18

Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Biopharmaceutics

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Contains Nonbinding Recommendations

Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is developed to provide manufacturers with recommendations for submission of new drug applications (NDAs), investigational new drug applications (INDs), or abbreviated new drug applications (ANDAs), as appropriate, for orally administered immediate-release (IR) drug products that contain highly soluble drug substances.[2] The guidance is intended to describe when a standard release test and criteria may be used in lieu of extensive method development and acceptance criteria-setting exercises. This guidance finalizes the guidance for industry on *Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs* (August 2015).[3] The revised title of this guidance better reflects its focus on the solubility of the drug substance in the drug product. Therefore, a direct reference to biopharmaceutics classification system (BCS) class 1 and class 3 is not necessary because permeability requirements are not within the focus of this guidance. The recommendations in this guidance clarify the recommendations in the guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997) for high solubility drug substances in IR drug products[4] that meet the conditions described in section III in this guidance. For drug substances that do not meet the conditions in this guidance, sponsors/applicants should follow the recommendations provided in the August 1997 guidance mentioned above.

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[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] *Drug substance* is an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient. 21 CFR 314.3(b).

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

[4] *Drug product* is a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. 21 CFR 314.3(b).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug substance under physiological conditions, and the permeation across the gastrointestinal membrane.[5,6] NDAs and ANDAs submitted to FDA contain bioavailability (BA) or bioequivalence (BE) data and in vitro dissolution data that, together with chemistry, manufacturing, and controls (CMC) data, characterize the quality and performance of the drug product. In vitro dissolution data are generally obtained from: *(1)* batches used in pivotal clinical and/or BA/BE studies, *(2)* batches used as stability registration batches, and *(3)* batches used in other human studies conducted during product development. In general, knowledge about the solubility, permeability, dissolution, and pharmacokinetics of a drug substance and drug product are considered when defining dissolution acceptance criteria as part of the drug approval process.

Immediate-release solid oral dosage form drug products containing high solubility drug substances are considered to be relatively low risk regarding the impact of dissolution on in vivo performance, provided the in vitro performance meets or exceeds the recommendations discussed herein.

This guidance establishes standard dissolution methodology and acceptance criteria that are appropriate for highly soluble drug substances that are formulated in IR dosage forms. The availability of these standards will facilitate the rapid development of dissolution methodology and related acceptance criteria with no requirement to show discriminatory ability of the dissolution method for these products during drug product development. In addition, these standards will facilitate FDA's evaluation of the data submitted in the application.

III. ELIGIBLE DRUG PRODUCTS

In addition to being an IR dosage form, the drug product should meet all of the following conditions in order for the dissolution standards in this guidance to apply. The FDA's Biopharmaceutics Classification System (BCS) guidance should be followed to establish that the drug product contains highly soluble drug substance.[7] Sponsors/applicants may contact FDA for

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[5] Amidon GL, Lennernas H, Shah VP, and Crison JR, 1995, A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability, Pharm Res, 12(3):413-420.

[6] Amidon GL, Lennernas H, Shah VP, and Crison JR, 2014, A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability, Pharm Res 12, 413-420, 1995-Backstory of BCS, The AAPS Journal, 16(5):894-898.

[7] See guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.*

assistance in applying the BCS guidance or in determining whether a particular drug product meets any of the particular conditions listed below.[8,9]

A. Dosage Form

This guidance applies to solid orally-administered IR drug products, such as tablets and capsules, that are meant to be swallowed. This guidance does not apply to orally disintegrating tablets (ODT).[10] However, if absorption from the oral cavity can be ruled out for the ODT, then the dissolution of the ODT may fall under this guidance. This guidance also does not apply to sublingual dosage forms which can be ODTs as well, as the scientific principles upon which this guidance is premised do not apply to the sublingual route of delivery, since sublingual dosage forms are intended for absorption in the oral cavity. This guidance may apply to chewable tablets[11] if the dissolution studies are conducted on the intact tablets and the product meets the conditions described in this guidance.

B. Solubility

To be considered a highly soluble drug product,**Error! Bookmark not defined.** the drug substance should be considered highly soluble with the highest drug product's strength[12] soluble in 250 mL or less of aqueous media over the pH range of 1 to 6.8 at 37°C ± 1°C. In other words, the highest strength divided by 250 should be less than or equal to the lowest solubility observed over the entire pH range of 1 - 6.8. For drug products where the highest single dose administered is higher than the highest strength, additional information may be necessary. The drug substance should be chemically stable at least up to the last dissolution time point in the specified dissolution media for the drug product, plus the interval of the longest analysis time including sample preparation and chromatography run times. Additional details regarding solubility testing methods can be found in the BCS guidance.

C. Therapeutic Index

This guidance does not apply to narrow therapeutic index (NTI) drug products because of the critical relationship between the bioavailable dose and clinical performance. NTI drug products pose higher therapeutic risks owing to their associated smaller differences between

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[8] For drug products to which the criteria in this guidance apply, the current methods listed in the FDA's Dissolution Methods Database will be replaced by the dissolution methods recommended in this guidance, on a case-by-case basis, upon submission of supplements in the corresponding NDA or ANDA submission. For products where the dissolution method described in a United States Pharmacopeia (USP) drug product monograph differs from the recommendations of this guidance, ANDA applicants may propose to use the approaches in this guidance as an updated method and seek revision of the relevant monograph.

[9] When the submission is for an NDA, contact the specific drug product's review division with questions. When the submission is for an ANDA, submit a Controlled Correspondence via email to GenericDrugs@fda.hhs.gov. For the definition of a *controlled correspondence* as well as the process to submit a *controlled correspondence*, see the guidance for industry *Controlled Correspondence Related to Generic Drug Development*.

[10] See guidance for industry *Orally Disintegrating Tablets.*

[11] See draft guidance for industry *Quality Attribute Considerations for Chewable Tablets.* When final, this guidance will represent the FDA's current thinking on this topic.

[12] For ANDAs, the highest strength for which approval is sought.

effective/ineffective and/or toxic/safe doses. The streamlined approach described in the guidance might not be able to detect the batch-to-batch difference(s) that might impact NTI performance with respect to safety or efficacy.[13]

D. Time to Maximum Plasma Concentration

If the time to maximum plasma concentration is critical to the intended use, this guidance does not apply. For example, labeling claims of early or rapid onset of action (e.g., rapid analgesia, rescue medications) exclude the drug product from adoption of the dissolution standard proposed herein.

E. Manufacturing and Testing History

Manufacturing and testing history, including stability testing throughout its shelf-life, should demonstrate that the drug product will meet the acceptance criteria in this guidance when using the standard dissolution testing conditions described herein.

F. Excipients

Excipients chosen for drug product formulation should be consistent with the design of IR drug products. Excipients should be included in quantities that are consistent with the excipients' labeled function and the target population. Excessive quantities of excipients, such as certain sweeteners and surfactants that can impact the drug absorption, may be problematic. For example, mannitol induces a dose proportional decrease in small intestinal transit time.[14] When this is a factor, we encourage sponsors/applicants to contact FDA[9] for guidance on a specific drug product.

IV. STANDARD DISSOLUTION TESTING CONDITIONS

If a drug product meets the eligibility requirements described in section III for a standard dissolution method and acceptance criterion, one of the following methods may be used.[15] Information on apparatus and number of units to test can be found in the USP General Chapter <711> Dissolution. The apparatus should be calibrated before use.[16]

[13] The current approach to establish bioequivalence of NTI drugs is described here: Yu LX, Jiang W, Zhang X, Lionberger R, Makhlouf F, Schuirmann DJ, Muldowney L, Chen M-L, Davit B, Conner D, Woodcock J, 2015, Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs, Clinical Pharmacology & Therapeutics, 97(3):286-291.

[14] Adkin, D.A., Davis, S.S., Sparrow, R.A., Huckle, P.D., Phillips, A.J., Wilding, I.R., 1995, The effect of different concentrations of mannitol in solution on small intestinal transit—implications for drug absorption, Pharm. Res., 12: 393–396.

[15] Shah V, Gurbarg M, Noory A, Dighe S, Skelly J, 1992, Influence of Higher Rates of Agitation on Release Patterns of Immediate-Release Drug Products, J Pharm Sci, 81(6): 500-503.

[16] See guidance for industry *The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (CGMP).*

A. Basket Method (USP apparatus 1)

- Stirring rate = 100 RPM
- 500 mL of 0.1N HCl in aqueous medium
- No surfactant in medium
- 37±0.5°C

B. Paddle Method (USP apparatus 2)

- Stirring rate = 50 RPM
- 500 mL of 0.1N HCl in aqueous medium
- No surfactant in medium
- 37±0.5°C

Although the hydrodynamics of the gastrointestinal tract are complicated and cannot be reproduced by the USP basket or paddle apparatus, a rotation speed of 100 RPM has been found to be discriminatory for the basket method. For the paddle method, 50 RPM (or 75 RPM with appropriate justification) can be discriminating while minimizing coning effects seen with lower stirring rates.[15] For the paddle method (USP apparatus 2), it is acceptable to add a few turns of a wire helix to ensure that capsule dosage forms are fully immersed in the dissolution bath. The acid conditions of the media reflect the conditions of the stomach whose volume is estimated at 250 mL when a glass of water is co-ingested with the oral dosage form. This volume is too low to use with the current basket and paddle apparatus; however, 500 mL of medium is commonly used and is an appropriate volume of medium for a highly soluble, rapidly dissolving drug substance. The 500 mL dissolution medium should be an appropriate volume to provide sink conditions for dissolution of the high soluble drug. Proper justification should be provided if 900 mL volume of the medium is used. Besides the recommended 0.1N HCl in aqueous medium, other dissolution media within the physiological pH range may be acceptable if appropriate justification is provided.

V. DISSOLUTION ACCEPTANCE CRITERIA

The drug product dissolution acceptance criterion is based on the high solubility of the drug substance. If an alternate acceptance criterion is proposed, the sponsor/applicant should provide additional data to support the proposed acceptance criterion. Additional supportive information could include appropriate in silico modeling in addition to dissolution performance data. For immediate release solid oral drug products containing a high solubility drug substance (as defined herein), the dissolution criterion is Q=80% in 30 minutes.

VI. POSTAPPROVAL CONSIDERATIONS

In regard to post-approval changes, with respect to the dissolution documentation that is needed to support the proposed change(s), the recommendations provided in the SUPAC-IR Guidance[17] should be followed.

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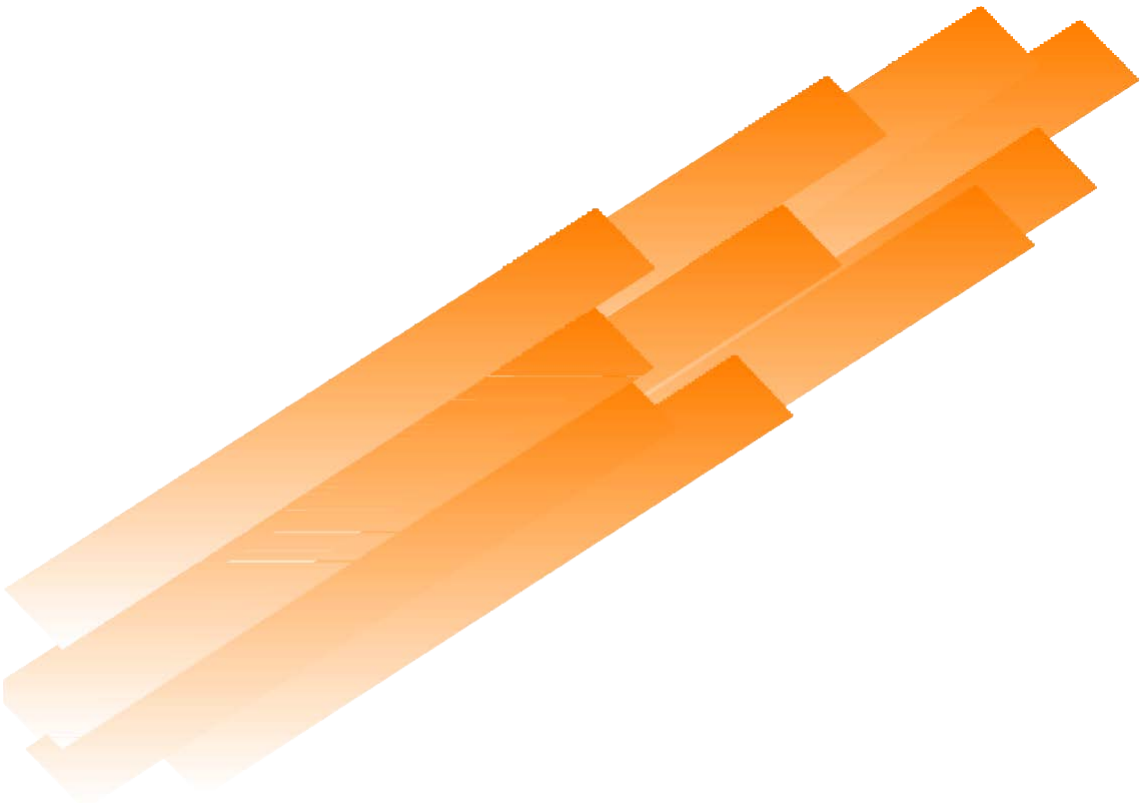
[17] See guidance for industry *Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*.

Guidance for Industry

Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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BP 2

Guidance for Industry

Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations

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Table of Contents

GUIDANCE FOR INDUSTRY[1]

Extended Release Oral Dosage Forms: Development, Evaluation, And Application Of In Vitro/In Vivo Correlations

I. INTRODUCTION

This guidance provides recommendations to pharmaceutical sponsors who intend to develop documentation in support of an in vitro/in vivo correlation (IVIVC) for an oral extended release (ER) drug product for submission in a new drug application (NDA), abbreviated new drug application (ANDA), or antibiotic drug application (AADA). The guidance presents a comprehensive perspective on (1) methods of developing an IVIVC and evaluating its predictability; (2) using an IVIVC to set dissolution specifications; and (3) applying an IVIVC as a surrogate for in vivo bioequivalence when it is necessary to document bioequivalence during the initial approval process or because of certain pre- or postapproval changes (e.g., formulation, equipment, process, and manufacturing site changes).

II. BACKGROUND

The concept of IVIVC, particularly for ER drug products, has been extensively discussed by pharmaceutical scientists. The ability to predict, accurately and precisely, expected bioavailability characteristics for an ER product from dissolution profile characteristics is a long sought after goal. Several workshops and publications have provided information in support of this goal. These are discussed briefly as follows:

- A report from a 1987 ASCPT/DIA/APS/FDA-sponsored workshop entitled *Report of the Workshop on CR Dosage Forms: Issues and Controversies* (1987) indicated that the state of science and technology at that time did not permit consistently meaningful IVIVC for ER dosage forms and encouraged IVIVC as a future objective. Dissolution testing was considered useful only for process control, stability, minor formulation changes, and manufacturing site changes.

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[1] This guidance has been prepared by the Extended Release Dissolution Working Group of the Biopharmaceutics Coordinating Committee (BCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on in vitro/in vivo correlations for extended release oral dosage forms. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the applicable statute, regulations, or both.

- A USP PF Stimuli Article in July 1988 established the classification of IVIVC into Levels A, B and C, which are currently in use.

- A report from a 1990 ASCPT/DIA/APS/FDA-sponsored workshop entitled *In vitro/In vivo Testing and Correlation for Oral Controlled/Modified Release Dosage Forms* (1990) concluded that, while the science and technology may not always permit meaningful IVIVC, the development of an IVIVC was an important objective on a product-by-product basis. Procedures for development, evaluation, and application of an IVIVC were described. Validation of dissolution specifications by a bioequivalence study involving two batches of product with dissolution profiles at the upper and lower dissolution specifications was suggested.

- USP Chapter 1088 similarly describes techniques appropriate for Level A, B, and C correlations and methods for establishing dissolution specifications.

- Further information related to IVIVCs was developed in a USP/AAPS/FDA-sponsored workshop, which resulted in a report entitled *Workshop II Report: Scale-up of Oral Extended Release Dosage Forms* (1993). This report identified the objectives of an IVIVC to be the use of dissolution as a surrogate for bioequivalency testing, as well as an aid in setting dissolution specifications. The report concluded that dissolution may be used as a sensitive, reliable, and reproducible surrogate for bioequivalence testing. The report gave support to the concepts of USP Chapter 1088 and further found that an IVIVC may be useful for changes other than minor changes in formulation, equipment, process, manufacturing site, and batch size.

These reports document increasing confidence in IVIVC to estimate the in vivo bioavailability characteristics for an ER drug product. In this regard, increased IVIVC activity in NDA submissions has been apparent. Still, the complete process of developing an IVIVC with high quality and predictability and identifying specific applications for such correlations has not been well defined.

As part of the process of developing this guidance, the Agency conducted several surveys of NDA submissions for ER drug products to find out the number of times that IVIVCs were developed. The first survey included NDA submissions from 1982-1992 and found 9 IVIVCs in 60 submissions. A more recent survey included NDA submissions from October 1994 to October 1995 and found 9 IVIVCs in 12 submissions.

This guidance is based on these prior deliberations and publications as well as on current understanding at the FDA and elsewhere on approaches to developing reliable and useful IVIVCs. This guidance describes the levels of correlations that can be established with varying degrees of usefulness, important considerations for in vivo and in vitro experimentation, evaluation of the correlation by focusing on the critical feature of predictability, and practical applications that can be achieved using the IVIVC. With the availability of this guidance, sponsors are encouraged to

develop IVIVCs for ER products in the expectation that the information will be useful in establishing dissolution specifications and will permit certain formulation and manufacturing changes without an in vivo bioequivalence study.

III. CATEGORIES OF IN VITRO/IN VIVO CORRELATIONS

A. Level A

A Level A correlation[2] is usually estimated by a two-stage procedure: deconvolution followed by comparison of the fraction of drug absorbed to the fraction of drug dissolved. A correlation of this type is generally linear and represents a point-to-point relationship between in vitro dissolution and the in vivo input rate (e.g., the in vivo dissolution of the drug from the dosage form). In a linear correlation, the in vitro dissolution and in vivo input curves may be directly superimposable or may be made to be superimposable by the use of a scaling factor. Nonlinear correlations, while uncommon, may also be appropriate.

Alternative approaches to developing a Level A IVIVC are possible. One alternative is based on a convolution procedure that models the relationship between in vitro dissolution and plasma concentration in a single step. Plasma concentrations predicted from the model and those observed are compared directly. For these methods, a reference treatment is desirable, but the lack of one does not preclude the ability to develop an IVIVC.

Whatever the method used to establish a Level A IVIVC, the model should predict the entire in vivo time course from the in vitro data. In this context, the model refers to the relationship between in vitro dissolution of an ER dosage form and an in vivo response such as plasma drug concentration or amount of drug absorbed.

B. Level B

A Level B IVIVC uses the principles of statistical moment analysis. The mean in vitro dissolution time is compared either to the mean residence time or to the mean in vivo dissolution time. A Level B correlation, like a Level A, uses all of the in vitro and in vivo data, but is not considered to be a point-to-point correlation. A Level B correlation does not uniquely reflect the actual in vivo plasma level curve, because a number of different in vivo curves will produce similar mean residence time values.

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[2] Level A correlations are the most common type of correlation developed in NDAs submitted to the FDA. Level B correlations are rarely seen in NDAs; multiple Level C correlations are seen infrequently.

C. Level C

A Level C IVIVC establishes a single point relationship between a dissolution parameter, for example, $t_{50\%}$, percent dissolved in 4 hours and a pharmacokinetic parameter (e.g., AUC, C_{max}, T_{max}). A Level C correlation does not reflect the complete shape of the plasma concentration time curve, which is the critical factor that defines the performance of ER products.

D. Multiple Level C

A multiple Level C correlation relates one or several pharmacokinetic parameters of interest to the amount of drug dissolved at several time points of the dissolution profile.

IV. GENERAL CONSIDERATIONS:

The following general statements apply in the development of an IVIVC in an NDA or ANDA/AADA:

- Human data should be supplied for regulatory consideration of an IVIVC.

- Bioavailability studies for IVIVC development should be performed with enough subjects to characterize adequately the performance of the drug product under study. In prior acceptable data sets, the number of subjects has ranged from 6 to 36. Although crossover studies are preferred, parallel studies or cross-study analyses may be acceptable. The latter may involve normalization with a common reference treatment. The reference product in developing an IVIVC may be an intravenous solution, an aqueous oral solution, or an immediate release product.

- IVIVCs are usually developed in the fasted state. When a drug is not tolerated in the fasted state, studies may be conducted in the fed state.

- Any in vitro dissolution method may be used to obtain the dissolution characteristics of the ER dosage form. The same system should be used for all formulations tested.

- The preferred dissolution apparatus is USP apparatus I (basket) or II (paddle), used at compendially recognized rotation speeds (e.g., 100 rpm for the basket and 50-75 rpm for the paddle). In other cases, the dissolution properties of some ER formulations may be determined with USP apparatus III (reciprocating cylinder) or IV (flow through cell).

  Appropriate review staff in CDER should be consulted before using any other type of apparatus.

- An aqueous medium, either water or a buffered solution preferably not exceeding pH 6.8, is recommended as the initial medium for development of an IVIVC. Sufficient data should be submitted to justify pH greater than 6.8. For poorly soluble drugs, addition of surfactant (e.g., 1% sodium lauryl sulfate) may be appropriate. In general, nonaqueous and hydroalcoholic systems are discouraged unless all attempts with aqueous media are unsuccessful. Appropriate review staff in CDER should be consulted before using any other media.

- The dissolution profiles of at least 12 individual dosage units from each lot should be determined. A suitable distribution of sampling points should be selected to define adequately the profiles. The coefficient of variation (CV) for mean dissolution profiles of a single batch should be less than 10%.

- A Level A IVIVC is considered to be the most informative and is recommended, if possible.

- Multiple Level C correlations can be as useful as Level A correlations. However, if a multiple Level C correlation is possible, then a Level A correlation is also likely and is preferred.

- Level C correlations can be useful in the early stages of formulation development when pilot formulations are being selected.

- Level B correlations are least useful for regulatory purposes.

- Rank order correlations are qualitative and are not considered useful for regulatory purposes.

V. DEVELOPMENT AND EVALUATION OF A LEVEL A IN VITRO/IN VIVO CORRELATION

A. Developing the Correlation

The most commonly seen process for developing a Level A IVIVC is to (1) develop formulations with different release rates, such as slow, medium, fast, or a single release rate if dissolution is condition independent; (2) obtain in vitro dissolution profiles and in vivo plasma concentration profiles for these formulations; (3) estimate the in vivo absorption or dissolution time course using an appropriate deconvolution technique for each formulation and subject (e.g., Wagner-Nelson, numerical deconvolution). These three steps establish the IVIVC model. Alternative approaches to developing Level A IVIVCs are possible. Further general information follows:

- The IVIVC relationship should be demonstrated consistently with two or more formulations with different release rates to result in corresponding differences in absorption profiles. Although an IVIVC can be defined with a minimum of two formulations with different release rates, three or more formulations with different release rates are recommended. Exceptions to this approach (i.e., use of only one formulation) may be considered for formulations for which in vitro dissolution is independent of the dissolution test conditions (e.g., medium, agitation, pH).

- Ideally, formulations should be compared in a single study with a crossover design.

- If one or more of the formulations (highest or lowest release rate formulations) does not show the same relationship between in vitro dissolution and in vivo performance compared with the other formulations, the correlation may still be used within the range of release rates encompassed by the remaining formulations.

- The in vitro dissolution methodology should adequately discriminate among formulations. Dissolution testing can be carried out during the formulation screening stage using several methods. Once a discriminating system is developed, dissolution conditions should be the same for all formulations tested in the biostudy for development of the correlation and should be fixed before further steps towards correlation evaluation are undertaken.

- During the early stages of correlation development, dissolution conditions may be altered to attempt to develop a 1-to-1 correlation between the in vitro dissolution profile and the in vivo dissolution profile.

- Time scaling may be used as long as the time scaling factor is the same for all formulations. Different time scales for each formulation indicate absence of an IVIVC.

B. Evaluating the Predictability of a Level A Correlation

An IVIVC should be evaluated to demonstrate that predictability of in vivo performance of a drug product from its in vitro dissolution characteristics is maintained over a range of in vitro dissolution release rates and manufacturing changes. Since the objective of developing an IVIVC is to establish a predictive mathematical model describing the relationship between an in vitro property and a relevant in vivo response, the proposed evaluation approaches focus on the estimation of predictive performance or, conversely, prediction error. Depending on the intended application of an IVIVC and the therapeutic index of the drug, evaluation of prediction error internally and/or externally may be appropriate. Evaluation of internal predictability is based on the initial data used to define the IVIVC model. Evaluation of external predictability is based on additional test data

sets. Application of one or more of these procedures to the IVIVC modeling process constitutes evaluation of predictability.

An important concept is that the less data available for initial IVIVC development and evaluation of predictability, the more additional data may be needed to define completely the IVIVC's predictability. Some combination of three or more formulations with different release rates is considered optimal.

Another significant factor is the range of release rates studied. The release rates, as measured by percent dissolved, for each formulation studied, should differ adequately (e.g., by 10%). This should result in in vivo profiles that show a comparable difference, for example, a 10% difference in the pharmacokinetic parameters of interest (C_{max} or AUC) between each formulation.

Methodology for the evaluation of IVIVC predictability is an active area of investigation and a variety of methods are possible and potentially acceptable. A correlation should predict in vivo performance accurately and consistently. Once this relationship has been achieved, in vitro dissolution can be used confidently as a surrogate for in vivo bioequivalence of ER drug products in the situations described below.

1. Experimental Data Considerations

    a. Dosage Form Properties: Dependence of In Vitro Release on Experimental Conditions

    Condition independent dissolution: If in vitro dissolution is shown to be independent of dissolution conditions (e.g., pH and agitation) and if the in vitro dissolution profile is shown to be equal to the in vivo absorption or in vivo dissolution profile, then the results for a single formulation (one release rate) may be sufficient. Evaluation of data for this formulation and evaluation of additional test data sets, as appropriate, for the purpose of estimation of internal and/or external predictability are recommended.

    Condition dependent dissolution: In all other instances where an IVIVC model is presented, results from a single formulation (one release rate) should be considered insufficient. To estimate internal and/or external predictability, evaluation of data from two or more formulations with different release rates is recommended.

    b. Internal and External Predictability

    Two distinct aspects of predictability can be considered. However, both aspects are not recommended in all instances.

Estimation of prediction error internally: The first aspect relates to evaluating how well the model describes the data used to define the IVIVC and is appropriate in all instances.

If formulations with three or more release rates are used to develop the IVIVC model, no further evaluation beyond this initial estimation of prediction error may be necessary for non-narrow therapeutic index drugs (Category 2 a and b applications, see page 12). However, depending on the results of this internal prediction error calculation, determination of prediction error externally may be appropriate.

If only two formulations with different release rates are used, the application of the IVIVC is further limited to Category 2a applications (see page 12). In this circumstance, determination of prediction error externally is recommended for complete evaluation and subsequent full application of the IVIVC.

Estimation of prediction error externally: The second aspect relates to how well the model predicts data when one or more additional test data sets are used that differ from those used to define the correlation. This is appropriate in some situations, particularly when only two formulations with different release rates are used to develop the IVIVC model, when calculation of prediction error internally is inconclusive, or when a narrow therapeutic index drug is studied.

The additional test data sets used for external prediction error calculation may have several differing characteristics compared to the data sets used in IVIVC development. Although formulations with different release rates provide the optimal test of an IVIVC's predictability, a formulation need not be prepared solely for this purpose. In the absence of such a formulation, data from other types of formulations may be considered. In each case, bioavailability data should be available for the data set under consideration.

The following represent, in decreasing order of preference, formulations that may be used to estimate prediction error externally:

- A formulation with a different release rate than those used in IVIVC development. The release rate of the test formulation may be either within or outside the range used to define the IVIVC relationship.

- A formulation with the same or similar release rate, but involving some change in manufacture of this batch (e.g., composition, process, equipment, manufacturing site).

- A formulation with the same or similar release rate obtained from another batch/lot with no changes in manufacturing.

c. Pharmacologic Properties of the Drug (Therapeutic Index)

Narrow therapeutic index drugs: If an IVIVC model is to be used in estimating the in vivo performance of formulations of narrow therapeutic index drugs, the model's predictability should be tested further with a data set that differs from those data sets used to define the correlation. In other words, the external predictability of the correlation should be evaluated.

Non-narrow therapeutic index drugs: If an IVIVC model is to be used in estimating the in vivo performance of formulations of non-narrow therapeutic index drugs, testing the model's predictability with a data set that differs from those data sets used to define the correlation may be desirable, but is not considered as important as for a narrow therapeutic index drug.

Note — If the classification of a drug as a narrow therapeutic index drug is uncertain, appropriate review staff in CDER should be consulted.

2. Methods for Evaluation of Predictability

The objective of IVIVC evaluation is to estimate the magnitude of the error in predicting the in vivo bioavailability results from in vitro dissolution data. This objective should guide the choice and interpretation of evaluation methods. Any appropriate approach related to this objective may be used for evaluation of predictability.

Internal predictability: All IVIVCs should be studied regarding internal predictability. One recommended approach involves the use of the IVIVC model to predict each formulation's plasma concentration profile (or C_{max} and/or AUC for a multiple Level C IVIVC) from each respective formulation's dissolution data. This is performed for each formulation used to develop the IVIVC model. The predicted bioavailability is then compared to the observed bioavailability for each formulation and a determination of prediction error is made.

Criteria

- Average absolute percent prediction error (% PE) of 10% or less for C_{max} and AUC establishes the predictability of the IVIVC. In addition, the % PE for each formulation should not exceed 15%.

- If these criteria are not met, that is, if the internal predictability of the IVIVC is inconclusive, evaluation of external predictability of the IVIVC should be performed as a final determination of the ability of the IVIVC to be used as a surrogate for bioequivalence.

External predictability: Most important when using an IVIVC as a surrogate for bioequivalence is confidence that the IVIVC can predict in vivo performance of subsequent lots of the drug product. Therefore, it may be important to establish the external predictability of the IVIVC. This involves using the IVIVC to predict the in vivo performance for a formulation with known bioavailability that was not used in developing the IVIVC model.

Criteria

- % PE of 10% or less for C_{max} and AUC establishes the external predictability of an IVIVC.

- % PE between 10 - 20% indicates inconclusive predictability and the need for further study using additional data sets. Results of estimation of PE from all such data sets should be evaluated for consistency of predictability.

- % PE greater than 20% generally indicates inadequate predictability, unless otherwise justified.

  With the exception of narrow therapeutic index drugs, the external predictability step in the IVIVC evaluation process may be omitted if the evaluation of internal predictability indicates acceptable % PE. However, when the evaluation of internal predictability is inconclusive, evaluation of external predictability is recommended.

VI. DEVELOPMENT AND EVALUATION OF A LEVEL C IN VITRO/IN VIVO CORRELATION

A single point Level C correlation allows a dissolution specification to be set at the specified time point. While the information may be useful in formulation development, waiver of an in vivo bioequivalence study (biowaiver) is generally not possible if only a single point correlation is available. A multiple point Level C correlation may be used to justify a biowaiver, provided that the correlation has been established over the entire dissolution profile with one or more pharmacokinetic parameters of interest. This could be achieved by correlating the amount dissolved at various time points with C_{max}, AUC, or any other suitable parameter. A relationship should be demonstrated at each time point with the same parameter such that the effect on the in vivo performance of any change in dissolution can be assessed. If such a multiple Level C

correlation is achievable, then the development of a Level A correlation is likely. A multiple Level C correlation should be based on at least three dissolution time points covering the early, middle, and late stages of the dissolution profile. The recommendations for assessing the predictability of Level C correlations will depend on the type of application for which the correlation is to be used. These methods and criteria are the same as those for a Level A correlation (see Section V B2).

VII. APPLICATIONS OF AN IVIVC

In vitro dissolution testing is important for (1) providing process control and quality assurance; (2) determining stable release characteristics of the product over time; and (3) facilitating certain regulatory determinations (e.g., absence of effect of minor formulation changes or of change in manufacturing site on performance). In certain cases, especially for ER formulations, the dissolution test can serve not only as a quality control for the manufacturing process but also as an indicator of how the formulation will perform in vivo. Thus, a main objective of developing and evaluating an IVIVC is to establish the dissolution test as a surrogate for human bioequivalence studies, which may reduce the number of bioequivalence studies performed during the initial approval process as well as with certain scale-up and postapproval changes. However, for the applications outlined below, the adequacy of the in vitro dissolution method to act as a surrogate for in vivo testing should be shown through an IVIVC for which predictability has been established.

A. Biowaivers for Changes in the Manufacturing of a Drug Product

1. Category 1: Biowaivers Without an IVIVC

For formulations consisting of beads in capsules, with the only difference between strengths being the number of beads, approval of lower strengths without an IVIVC is possible, provided bioavailability data are available for the highest strength.

Where the guidance for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Postapproval changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* recommends a biostudy, biowaivers for the same changes made on lower strengths are possible without an IVIVC if (1) all strengths are compositionally proportional or qualitatively the same, (2) in vitro dissolution profiles of all strengths are similar, (3) all strengths have the same release mechanism, (4) bioequivalence has been demonstrated on the highest strength (comparing changed and unchanged drug product), and (5) dose proportionality has been demonstrated for this ER drug product. In the last circumstance (5), documentation of dose proportionality may not be necessary if bioequivalence has been demonstrated on the highest and lowest strengths of the drug product,

comparing changed and unchanged drug product for both strengths, as recommended in SUPAC-MR.

For the above situations, waivers can be granted without an IVIVC if dissolution data are submitted in the application/compendial medium and in three other media (e.g., water, 0.1N HCl, and USP buffer at pH 6.8, comparing the drug product after the change to the drug product before the change).

Biowaivers, as defined in SUPAC-MR, that do not necessitate either bioequivalence testing or an IVIVC will likely be granted in preapproval situations for both narrow and non-narrow therapeutic index ER drug products if dissolution data, as described in SUPAC-MR, are submitted.

Comparison of dissolution profiles: Dissolution profiles can be compared using model independent or model dependent methods. A model independent approach using a similarity factor, and comparison criteria are described in SUPAC-MR.

2. Category 2: Biowaivers Using an IVIVC: Non-Narrow Therapeutic Index Drugs

   a. Two Formulations/Release Rates

   A biowaiver will likely be granted for an ER drug product using an IVIVC developed with two formulations/release rates for (1) Level 3 manufacturing site changes as defined in SUPAC-MR; (2) Level 3 nonrelease controlling excipient changes as defined in SUPAC-MR, with the exception of complete removal or replacement of excipients (see below).

   b. Three Formulations/Release Rates

   A biowaiver will likely be granted for an ER drug product using an IVIVC developed with three formulations/release rates (or developed with two formulations/release rates with establishment of external predictability) for (1) Level 3 process changes as defined in SUPAC-MR; (2) complete removal of or replacement of nonrelease controlling excipients as defined in SUPAC-MR; and (3) Level 3 changes in the release controlling excipients as defined in SUPAC-MR.

   c. Biowaivers for Lower Strengths

   If an IVIVC is developed with the highest strength, waivers for changes made on the highest strength and any lower strengths may be granted if

these strengths are compositionally proportional or qualitatively the same, the in vitro dissolution profiles of all the strengths are similar, and all strengths have the same release mechanism.

d. Approval of New Strengths

This biowaiver is applicable to strengths lower than the highest strength, within the dosing range that has been established to be safe and effective, if the new strengths are compositionally proportional or qualitatively the same; have the same release mechanism; have similar in vitro dissolution profiles; and are manufactured using the same type of equipment and the same process at the same site as other strengths that have bioavailability data available.

For generic products to qualify for this biowaiver, one of the following situations should exist:

- Bioequivalence has been established for all strengths of the reference listed product.

- Dose proportionality has been established for the reference listed product, and all reference product strengths are compositionally proportional or qualitatively the same, have the same release mechanism, and the in vitro dissolution profiles of all strengths are similar.

- Bioequivalence is established between the generic product and the reference listed product at the highest and lowest strengths and, for the reference listed product, all strengths are compositionally proportional or qualitatively the same, have the same release mechanism, and the in vitro dissolution profiles are similar.

Obtaining category 2d biowaivers: The difference in predicted means of C_{max} and AUC should be no more than 10%, based on dissolution profiles of the highest strength and the lower strength product.

e. Changes in Release Controlling Excipients

Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.

f. Obtaining Category 2a, 2b, and 2c Biowaivers:

The difference in predicted means of C_{max} and AUC should be no more than 20% from that of the reference product and, where appropriate, the new formulation should meet the application/compendial dissolution specifications.

3. Category 3: Biowaivers Using an IVIVC: Narrow Therapeutic Index Drugs

If external predictability of an IVIVC is established, the following waivers will likely be granted if at least two formulations/release rates have been studied for the development of the IVIVC.

a. Situations in Which Biowaivers May Be Granted

A biowaiver will likely be granted for an ER drug product using an IVIVC for (1) Level 3 process changes as defined in SUPAC-MR; (2) complete removal of or replacement of non-release controlling excipients as defined in SUPAC-MR; and (3) Level 3 changes in the release controlling excipients as defined in SUPAC-MR.

b. Biowaivers for Lower Strengths

If an IVIVC is developed with the highest strength, waivers for changes made on the highest strength and any lower strengths may be granted, if these strengths are compositionally proportional or qualitatively the same, the in vitro dissolution profiles of all the strengths are similar, and all strengths have the same release mechanism.

c. Approval of New Strengths

This biowaiver is applicable to strengths lower than the highest strength, within the dosing range that has been established to be safe and effective, provided that the new strengths are compositionally proportional or qualitatively the same, have the same release mechanism, have similar in vitro dissolution profiles, and are manufactured using the same type of equipment, and the same process at the same site as other strengths that have bioavailability data available.

For generic products to qualify for this biowaiver, one of the following situations should exist:

- Bioequivalence has been established for all strengths of the reference listed product.

- Dose proportionality has been established for the reference listed product, all reference product strengths are compositionally proportional or qualitatively the same and have the same release mechanism, and the in vitro dissolution profiles of all strengths are similar.

- Bioequivalence is established between the generic product and the reference listed product at the highest and lowest strengths and, for the reference listed product, all strengths are compositionally proportional or qualitatively the same and have the same release mechanism, and the in vitro dissolution profiles are similar.

Obtaining category 3c biowaivers: The difference in predicted means of C_{max} and AUC should be no more than 10%, based on dissolution profiles of the highest strength and the lower strength product.

d. Changes in Release Controlling Excipients

- Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.

e. Obtaining Category 3a and 3b Biowaivers:

The difference in predicted means of C_{max} and AUC should be no more than 20% from that of the reference product and, where appropriate, the new formulation meets the application/compendial dissolution specifications.

4. Category 4: Biowaivers When In Vitro Dissolution Is Independent of Dissolution Test Conditions

Situations in which biowaivers are likely to be granted for both narrow and non-narrow therapeutic index drugs:

a. Category 2 and Category 3 biowaivers are likely to be granted with an IVIVC established with one formulation/release rate.

Biowaivers may be granted if dissolution data are submitted in application/compendial medium and in three other media (e.g., water, 0.1 N HCl, USP buffer at pH 6.8) and the following conditions apply:

- In vitro dissolution should be shown to be independent of dissolution test conditions after change is made in drug product manufacturing.

- Comparison of dissolution profiles

Dissolution profiles can be compared using model independent or model dependent methods. A model independent approach using a similarity factor and comparison criteria is described in SUPAC-MR.

b. Obtaining Category 4 Biowaivers

The difference in predicted means of C_{max} and AUC should be no more than 20% from that of the reference product and, where appropriate, the new formulation should meet the application/compendial dissolution specifications.

5. Category 5: Situations for which an IVIVC Is Not Recommended

a. Approval of a new formulation of an approved ER drug product when the new formulation has a different release mechanism.

b. Approval of a dosage strength higher or lower than the doses that have been shown to be safe and effective in clinical trials.

c. Approval of another sponsor's ER product even with the same release controlling mechanism.

d. Approval of a formulation change involving a nonrelease controlling excipient in the drug product that may significantly affect drug absorption.

B. Setting Dissolution Specifications

In vitro dissolution specifications should generally be based on the performance of the clinical/bioavailability lots. These specifications may sometimes be widened so that scale-up lots, as well as stability lots, meet the specifications associated with the clinical/bioavailability lots. This approach is based on the use of the in vitro dissolution test as a quality control test without any in vivo significance, even though in certain cases (e.g., ER formulations), the rate limiting step in the absorption of the drug is the dissolution of the drug from the formulation. An IVIVC adds in vivo relevance to in vitro dissolution specifications, beyond batch-to-batch quality control. In this approach, the in vitro dissolution test becomes a meaningful predictor of in vivo performance of the

formulation, and dissolution specifications may be used to minimize the possibility of releasing lots that would be different in in vivo performance.

1. Setting Dissolution Specifications Without an IVIVC

- The recommended range at any dissolution time point specification is ± 10% deviation from the mean dissolution profile obtained from the clinical/bioavailability lots.

- In certain cases, reasonable deviations from the ± 10 % range can be accepted provided that the range at any time point does not exceed 25%. Specifications greater than 25% may be acceptable based on evidence that lots (side batches) with mean dissolution profiles that are allowed by the upper and lower limit of the specifications are bioequivalent.

- Specifications should be established on clinical/bioavailability lots. Widening specifications based on scale-up, stability, or other lots for which bioavailability data are unavailable is not recommended.

- A minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the dissolution profile. The last time point should be the time point where at least 80% of drug has dissolved. If the maximum amount dissolved is less than 80%, the last time point should be the time when the plateau of the dissolution profile has been reached.

- Specifications should be established based on average dissolution data for each lot under study, equivalent to USP Stage 2 testing. Specifications allow that all lots to pass at Stage 1 of testing may result in lots with less than optimal in vivo performance passing these specifications at USP Stage 2 or Stage 3.

- USP acceptance criteria for dissolution testing are recommended unless alternate acceptance criteria are specified in the ANDA/NDA.

2. Setting Dissolution Specifications Where an IVIVC Has Been Established

Optimally, specifications should be established such that all lots that have dissolution profiles within the upper and lower limits of the specifications are bioequivalent. Less optimally but still possible, lots exhibiting dissolution profiles at the upper and lower dissolution limits should be bioequivalent to the clinical/bioavailability lots or to an appropriate reference standard.

a. Level A Correlation Established

- Specifications should be established based on average data.

- A minimum of three time points is recommended to establish the specifications. These time points should cover the early, middle and late stages of the dissolution profile. The last time point should be the time point where at least 80% of drug has dissolved. If the maximum amount dissolved is less than 80%, then the last time point should be the time where the plateau of the dissolution profile has been reached.

- Calculate the plasma concentration time profile using convolution techniques or other appropriate modeling techniques and determine whether the lots with the fastest and slowest release rates that are allowed by the dissolution specifications result in a maximal difference of 20% in the predicted C_{max} and AUC.

- An established IVIVC may allow setting wider dissolution specifications. This would be dependent on the predictions of the IVIVC (i.e., 20% differences in the predicted C_{max} and AUC).

- USP acceptance criteria for dissolution testing are recommended unless alternate acceptance criteria are specified in the ANDA/NDA.

b. Multiple Level C Correlation Established

- If a multiple point Level C correlation has been established, establish the specifications at each time point such that there is a maximal difference of 20% in the predicted C_{max} and AUC.

- Additionally, the last time point should be the time point where at least 80% of drug has dissolved.

c. Level C Correlation Based on Single Time Point Established

This one time point may be used to establish the specification such that there is not more than a 20% difference in the predicted AUC and C_{max}. At other time points, the maximum recommended range at any dissolution time point specification should be ± 10% of label claim deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Reasonable deviations from ± 10% may be acceptable if the range at any time point does not exceed 25%.

3. Setting Specifications Based on Release Rate

If the release characteristics of the formulation can be described by a zero-order process for some period of time (e.g., 5%/hr from 4 to 12 hours), and the dissolution profile appears to fit a linear function for that period of time, a release rate specification may be established to describe the dissolution characteristics of that formulation. A release rate specification may be an addition to the specifications established on the cumulative amount dissolved at the selected time points. Alternatively, a release the rate specification may be the only specification except for the specification for time when at least 80% of drug has dissolved.

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DEFINITION OF TERMS

Batch: A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits *(21 CFR 210.3(b)(2))*.

Batch formula (composition): A complete list of the ingredients and their amounts to be used for the manufacture of a representative batch of the drug product. All ingredients should be included in the batch formula whether or not they remain in the finished product *(Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products, FDA, February 1987)*.

Bioavailability: The rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action *(21 CFR 320.1(a))*.

Biobatch: A lot of drug product formulated for purposes of pharmacokinetic evaluation in a bioavailability/bioequivalency study. This lot should be 10% or greater than the proposed commercial production batch or at least 100,000 units, whichever is greater.

Bioequivalent drug products: Pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied *(21 CFR 320.1(e))*.

Convolution: Prediction of plasma drug concentrations using a mathematical model based on the convolution integral. For example, the following convolution integral equation may be used to predict the plasma concentration ($c(t)$) resulting from the absorption rate time course (r_{abs}):

$$c(t) = \int_0^t c_o(t-u)\, r_{abs}(u)\, du$$

The function c_o represents the concentration time course that would result from the instantaneous absorption of a unit amount of drug and can be estimated from either i.v. bolus data, oral solution, suspension or rapidly releasing (in vivo) immediate release dosage forms.

Correlation: As used in this guidance, a relationship between in vitro dissolution rate and in vivo input (absorption) rate.

Deconvolution: Estimation of the time course of drug input (usually in vivo absorption or dissolution) using a mathematical model based on the convolution integral. For example, the

absorption rate time course (r_{abs}) that resulted in the plasma concentrations ($c(t)$) may be estimated by solving the following convolution integral equation for r_{abs}:

$$c(t) = \int_0^t c_o(t-u)\, r_{abs}(u)\, du$$

The function c_o represents the concentration time course that would result from the instantaneous absorption of a unit amount of drug and is typically estimated from either i.v. bolus data, oral solution, suspension or rapidly releasing (in vivo) immediate release dosage forms.

Development: Establishing an in vitro/in vivo correlation.

Drug product: A finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients *(21 CFR 314.3(b))*.

Extended release dosage form: A dosage form that allows a reduction in dosing frequency as compared to that presented by a conventional dosage form, e.g., a solution or an immediate release dosage form.

Evaluation: In the context of in vitro/in vivo correlation, a broad term encompassing experimental and statistical techniques used during development and evaluation of a correlation which aid in determining the predictability of the correlation.

Formulation: A listing of the ingredients and composition of the dosage form.

In vitro/in vivo correlation: A predictive mathematical model describing the relationship between an in vitro property of an extended release dosage form (usually the rate or extent of drug dissolution or release) and a relevant in vivo response, e.g., plasma drug concentration or amount of drug absorbed.

In vivo dissolution: The process of dissolution of drug in the gastro-intestinal tract.

In vitro release: Drug dissolution (release) from a dosage form as measured in an in vitro dissolution apparatus.

In vivo release: In vivo dissolution of drug from a dosage form as determined by deconvolution of data obtained from pharmacokinetic studies in humans (patients or healthy volunteers).

Level A correlation: A predictive mathematical model for the relationship between the entire in vitro dissolution/release time course and the entire in vivo response time course, e.g., the time course of plasma drug concentration or amount of drug absorbed.

Level B correlation: A predictive mathematical model for the relationship between summary parameters that characterize the in vitro and in vivo time courses, e.g., models that relate the mean in vitro dissolution time to the mean in vivo dissolution time, the mean in vitro dissolution

time to the mean residence time in vivo, or the in vitro dissolution rate constant to the absorption rate constant.

Level C correlation: A predictive mathematical model of the relationship between the amount dissolved in vitro at a particular time (or the time required for in vitro dissolution of a fixed percent of the dose, e.g., $T_{50}\%$) and a summary parameter that characterizes the in vivo time course (e.g., C_{max} or AUC).

Lot: A batch, or a specific identified portion of a batch, having uniform character and quality within specified limits or, in the case of a drug product produced by continuous process, a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits *(21 CFR 210.3(b)(10))*.

Mean absorption time: The mean time required for drug to reach systemic circulation from the time of drug administration. This term commonly refers to the mean time involved in the in vivo release and absorption processes as they occur in the input compartment and is estimated as MAT = MRT_{oral} - $MRT_{i\,v}$

Mean in vitro dissolution time: The mean time for the drug to dissolve under in vitro dissolution conditions. This is calculated using the following equation:

$$MDT_{vitro} = \frac{\int_o (M - M(t))\,dt}{M}$$

Mean in vivo dissolution time: For a solid dosage form: $MDT_{solid} = MRT_{solid} - MRT_{solution}$. This reflects the mean time for drug to dissolve in vivo.

Mean residence time: The mean time that the drug resides in the body. MRT may also be the mean transit time. MRT = AUMC/AUC.

Narrow therapeutic index drugs: Drugs having, for example, less than a two-fold difference in the minimum toxic concentrations and the minimum effective concentrations *(21 CFR 320.33 (c))*.

Nonrelease controlling excipient (noncritical compositional variable): An inactive ingredient in the final dosage form that does not significantly affect the release of the active drug substance from the dosage form.

Predictability: Verification of the model's ability to describe in vivo bioavailability results from a test set of in vitro data (external predictability) as well as from the data that was used to develop the correlation (internal predictability).

Percent prediction error:

$$\% PE = [(\text{Observed value} - \text{Predicted value}) / \text{Observed value}] \times 100$$

Release controlling excipient (critical compositional variable): An inactive ingredient in the final dosage form that functions primarily to extend the release of the active drug substance from the dosage form.

Release mechanism: The process by which the drug substance is released from the dosage form.

Release rate: Amount of drug released per unit of time as defined by in vitro or in vivo testing.

Statistical moments: Parameters that describe the characteristics of the time courses of plasma concentration (area, mean residence time, and variance of mean residence time) and of urinary excretion rate.