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Workshop Report

AAPS/USP Workshop on Dissolution Calibration and Testing

OVERVIEW

The AAPS/USP Workshop on Dissolution Calibration and Testing was held September 28-29 in Crystal City, Virginia. The objectives of the day and a half workshop were to: 1) provide "how-to" instruction for dissolution calibration using USP calibrators; 2) provide a forum for the debate on the merit of dissolution calibration; 3) present alternative methods for dissolution calibration; and 4) provide a tutorial on the basics of *in vivo/in vitro* correlations.

The workshop was divided into three sessions. The first session, entitled "Dissolution Calibration: Testing," covered the history, the process, some problems, reasons for, and regulations governing calibration of dissolution testing apparatuses. The second session addressed "Dissolution Calibration: Controversy" and focussed more specifically on the difficulties with the current dissolution calibration process. The morning of the second day was devoted to a session entitled, "*In Vivo/In Vitro* Correlations - A Tutorial" which pointed up the importance of having consistent dissolution data to develop correlations. Each session was followed by an extensive audience participation panel discussion.

DISSOLUTION CALIBRATION: TESTING

History

Thomas A. Morgan, of Glaxo Wellcome, opened the first session of the workshop with his talk entitled, "History of Dissolution Calibration." Morgan provided an overview of the historical context into which dissolution calibration fits. Starting with the late 1800's when it first became apparent that the dissolution of a pill was a prerequisite for drug absorption, Dr. Morgan traced the developments that led to the joint USP-NF panel which recognized the need to test individual dosage units in order to assure drug effectiveness. These panel recommendations led, in the 1970's, to official dissolution tests for twelve monographs using the rotating basket apparatus. Recognition of laboratory to laboratory variability and apparatus to apparatus variability led the USP Committee of Revision Subcommittee on General Chapters to develop "calibrators" for dissolution testing and to recommend the use of two apparatuses, the rotating basket and the rotating paddle. The decade of the 70's saw both the FDA and the USP publishing opinions and standards for dissolution testing, as well as the development by a PMA collaborative study of the prednisone and salicylic acid calibrators used today. Calibration criteria were set which all equipment must meet to be used for compendial dissolution testing. These criteria included four tests per apparatus type with both disintegrating (prednisone) and non-disintegrating (salicylic acid) tablets at 50 and 100 rpm for each tablet type. It was left to the individual labs to determine the frequency with which they recalibrated their equipment, but six months was suggested. All subsequent lots of USP calibrator tablets were qualified by industry-based collaborative studies using the same statistical criteria to establish the limits of acceptability that had been used in the original lots. There have been six lots of prednisone and eight lots of salicylic acid calibrators since the inception of the program. Morgan closed his talk by posing several questions about the future of dissolution calibration: What is the proper function of calibrators? How many conditions are required to fulfill those functions? Are the criteria developed fifteen years ago still appropriate? What characteristics should future calibrators have? Should they be only for variables that cannot be measured in any other way? Who should take the lead in optimizing dissolution calibration?

Industrial Perspective

Gregory P. Martin of Merck Research Laboratory next provided a "Tutorial on Dissolution Calibration and Testing (An Industrial Perspective)." The three reasons presented for calibrating a dissolution apparatus are to demonstrate that the apparatus is functioning acceptably, to comply with compendial requirements, and to allow the comparison of data generated on multiple formulation batches or in multiple laboratories. He covered how to calibrate a dissolution apparatus, including how to check the mechanical properties of the apparatus for such factors as temperature or vibration, and how to perform the apparatus suitability tests using calibrator tablets. Martin emphasized the importance of deaeration of the media to obtain consistent results. He also briefly discussed the calibration of apparatus 3, a reciprocating cylinder device, using extended-release calibrators and pointed out the need for an in-house calibrator when testing extended-release products.

Calibration Problems

Vivian A. Gray of the United States Pharmacopeial Convention, Inc. (USP) addressed "How to Resolve USP Apparatus 1 and 2 Calibration Problems and Validate USP Dissolution and Drug Release Tests." She reviewed what to do in the case that a calibrator tablet test result falls outside of the certified acceptance ranges. Gray emphasized that retesting continuously without first examining the system is not a scientifically sound approach to dissolution calibration testing. Major sources of error, in her experience, are vibration effects, both in the apparatus itself and in its surrounding environment, and improper deaeration. Since bubbles adhering to the basket mesh, or to the tablet itself, can affect results, Gray covered in detail the proper ways to deaerate the medium. She also detailed other prevalent sources of error in apparatus suitability tests, including dirty or irregularly shaped vessels, the tendency of the calibrator tablets to take on water if not properly stored, careless filtering, inaccurately prepared buffers, and problems with routine wear and tear on paddles an baskets.

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FDA Requirements

The final speaker of the morning session, Larry Ouderkirk of the FDA, gave an "Overview of Dissolution Requirements for NDA and ANDA Drug Products." The Agency views the purposes of dissolution testing to be fourfold: to assist in formulation development, as a quality control tool, as a regulatory requirement, and as a legal requirement. In formulation development, dissolution testing can aid in the selection of excipients, help optimize the manufacturing process, and enable formulation of the test product to match the release of the reference product. As a quality control tool, dissolution testing provides a check on manufacturing parameters, ensures lot-to-lot uniformity, and is important in assessing the stability of the product. Dissolution testing is a key element in pre-approval BA/BE requirements as well as post-approval changes. Finally, the approved product must satisfy the compendial requirements for dissolution. FDA requires dissolution/release testing for oral immediate-release products, including solid oral dosage forms and oral suspension, and oral modified-release products, including delayed-release and extended-release tablets and capsules. Ouderkirk reviewed those NDA and ANDA products for which both dissolution testing and *in vivo* studies are required for approval as well as those products for which dissolution studies alone are sufficient. He also reviewed the post-approval changes for which dissolution testing is sufficient. Ouderkirk reviewed the process involved in setting dissolution specifications for immediate-release solid oral dosage forms, immediate-release oral suspensions, immediate-release chewable sublingual tablets, immediate-release hard and soft gelatin capsules, delayed-release oral dosage forms, and extended release dosage forms. This included the type of apparatus, the characteristics of the media, and the establishment of tolerances. For extended-release formulations these specifications are set manufacturer by manufacturer based on the release mechanism of the drug product using a method developed by the sponsor. Ouderkirk raised what he saw as some of the current and future issues in dissolution, such as the biopharmaceutics classification system based on solubility and permeability of the drug product, newer statistical methods to evaluate dissolution data, mapping side batches as an alternative to *in vivo/in vitro* correlations for immediate-release products, and the soon-to-be-issued Scale-up and Post-approval Changes Guidance for Immediate Release Solid Oral Dosage Forms.

DISSOLUTION CALIBRATION: CONTROVERSY

European Perspective

The afternoon session was opened by Johannes Kramer of Deutsches Arzneiprufungsinstitut and he provided the "European Perspective - American and European Equipment Calibration Issues." Kramer noted that small differences in the specifications of equipment still exist between Europe and the U.S. Not the least of the problems is that equipment in Europe is manufactured using the metric system while that in the U.S. is not. The only compendial reference in Europe is the General Monograph which does not call for a system suitability test, i.e. calibration of the dissolution testing equipment. The European General Monograph describes the specifications not only for the basket and paddle apparatuses, but also for the flow-through cell. Currently, a working group from FIP is preparing a calibrator for this type of dissolution testing device.

Industry Views

Tim McCormick of DuPont Merck Pharmaceutical Co., followed with the "Industry Perspective - Issues and Difficulties with Dissolution Calibration." In order to provide background for a debate on the merit of dissolution calibration and to present alternative methods, McCormick conducted an informal survey of the members of the National Stability Discussion Group and readers of *Dissolution Technologies*. Respondents represented industry, government, and equipment manufacturers. Almost three-fourths of the respondents calibrate their apparatuses every 6 months. A third of the respondents calibrate their equipment to insure proper performance of the system, while 50% calibrate either because it is a USP requirement or is needed for GMP compliance. When asked whether the USP calibrator tablets were necessary and/or useful for dissolution apparatus calibration, 27% responded that they were necessary while 19% responded that they were not. Twenty-one percent thought they were useful while 33% did not. Forty-one percent of the respondents felt that using mechanical measurements and tightening the mechanical tolerances would be a useful alternative to the calibrator tablets. An overwhelming 94% of the respondents indicated that they had had difficulty in meeting the USP calibrator tablet specifications, more so with prednisone than with the salicylic acid tablets. From this survey, McCormick concluded that the view of industry is that a calibrator tablet is necessary, but the current USP calibrators are no longer adequate. New calibrator tablets should be more sensitive to physical parameters and less sensitive to extraneous factors. In addition, the number of tests required should be reduced and a more efficient deaeration technique should be developed, especially for large volumes.

Physicochemical and Fluid Mechanical Principles

John W. Mauger, Ph.D. of the University of Utah presented a talk entitled, "Physicochemical and Fluid Mechanical Principles Applied to Dissolution Testing." According to Mauger, dissolution performance is influenced not only by factors inherent in the dosage form, but also by the factors associated with the diffusion method. Thus, dissolution performance is a function of fluid velocity in a known flow field, shear at the dissolving surface, and fluid viscosity, and these factors can vary dependent upon the apparatus used. He outlined some of the desirable characteristics of a dissolution apparatus in terms of fluid mechanical principles and discussed fluid flow measurement methods using anemometry.

Role of NCDA-2 Calibrator Tablets

Henry D. Drew, Ph.D. of the FDA, addressed "The Role of Calibrator Tablets for Determining Dissolution Testing System Suitability: USP Apparatus I and II." For more

than seventeen years, his laboratory has been using an in-house calibrator, NCDA-2. This tablet has been an extremely stable formulation and no tablet has failed the dissolution test. Because NCDA-2 was taken from a failed sample submitted to the FDA, there is a finite supply and Drew discussed efforts by Shangraw and co-workers at the University of Maryland to replicate the formulation and performance in new tablets. Most likely due to differences in excipients and manufacturing conditions in the ensuing years, the new tablets dissolve four times more quickly than NCDA-2 despite the formulation being, on paper, identical. Drew also described the deaeration procedure used in his laboratory which remains stable for up to five days, is done at room temperature and is more amenable to use on large volumes than is the USP-recommended method. This degassing procedure has been validated against the USP procedure. Drew provided samples of the calibrator tablets for workshop attendees.

IN VIVO/IN VITRO CORRELATIONS

Are They Necessary?

Session III on the morning of the second day switched gears slightly to present a tutorial on *in vivo/in vitro* correlations. The morning began with Thomas S. Foster, Pharm.D. of the University of Kentucky speaking about "*In vivo/in vitro* Correlations: In Sync with Pharmaceutical Care?" Given the substantial increase in the availability of multi-source drugs, corporate mergers leading to changes in manufacturing sites and new sources of drug substance, outsourcing for the manufacture of dosage forms, and the advent of new manufacturing technologies, *in vivo/in vitro* correlations are becoming increasingly important. The problem is how to correlate *in vitro* properties such as physical/chemical characteristics, stability, solubility, water content, and extent of dissolution to *in vivo* performance when the latter is impacted by enzymes, motility, drug/food interactions, age effects, absorption rate, and the physiology of the GI tract. Foster discussed the USP correlation levels A, B, and C. A level A correlation, the most preferred, is a point-to-point correlation where the dissolution curve and the *in vivo* input rates are superimposable. A level A correlation may be a surrogate for bioequivalence trials so that minor manufacturing site changes would not require a full biostudy. A level B correlation is arrived at by statistical moment analysis where the mean *in vitro* dissolution correlates to *in vivo* mean residence or dissolution time. A level C correlation relates one dissolution point to a single pharmacokinetic parameter. While a level C correlation is not useful in production changes, it may be useful in design and/or formulation decisions.

Industry Perspective

In his talk entitled, "*In Vivo/In Vitro* Correlations: An Industry Perspective," Jack Rosen of Schering-Plough Corporation, addressed dissolution requirements and product development. He talked about the development of two different kinds of extended release dosage forms. In one, controlled release is achieved by varying the amount of polymer matrix in the dosage form. For this dosage form, a dissolution study correlated with *in vivo* performance characteristics. In the second example, an enteric coated tablet, release is controlled by the amount of barrier coat. Alternate dissolution measurement methods had to be developed for this dosage form because the USP apparatuses 1 and 2 could not adequately measure it.

Controlled Release Dosage Forms

Russell J. Rackley, Ph.D. of Ciba-Geigy Corporation presented a tutorial entitled, "*In Vivo/In Vitro* Correlations for Controlled Release Dosage Forms." He defined an *in vivo/in vitro* correlation in the biopharmaceutical context as "the establishment of a relationship between a biological property produced by a dosage form, and a physicochemical characteristic of the same dosage form." An *in vivo/in vitro* correlation may: serve as a surrogate to bioequivalence studies required for minor post-approval changes; serve as a quality control tool to justify dissolution testing specifications and methods by demonstrating their relevance to *in vivo* performance; aid in the design of formulation release-time profiles by predicting *in vivo* performance; and be used to identify appropriate dissolution test conditions for a formulation which is relevant to *in vivo* performance. Despite their value, there are limitations to *in vivo/in vitro* correlations. In particular, the release from the dosage form should be the rate-limiting step in absorption. While this is generally true for extended-release formulations, immediate-release dosage forms tend to be more prone to absorption rate limitations. Furthermore, a narrow therapeutic index may limit the use of dissolution as a surrogate for bioequivalence, no matter how good the *in vivo/in vitro* correlation. Rackley gave several examples of using convolution and deconvolution of concentration-time/dissolution-time profiles to establish *in vivo/in vitro* correlations, concluding that much work remains to be done to arrive at a statistical-based approach to setting dissolution specifications.

FDA Perspectives

The final speaker, Henry J. Malinowski, Ph.D. of the FDA, gave the "FDA Perspective on *In Vivo/In Vitro* Correlations." He reviewed the uses of dissolution testing, but pointed out that the tests can be overly discriminatory and pick out differences that are not significant. Malinowski feels that *in vitro* dissolution is one of the most important tests, even though there is no complete assurance that *in vitro* dissolution exactly reflect *in vivo* dissolution. He ranked the types of bioequivalence testing on a usefulness scale of one to 10 where a bioequivalency study ranked as 10 and an assay ranked as zero. On this scale, a dissolution profile ranked as five while a dissolution study based on an *in vivo/in vitro* correlation ranked as ten. He then reviewed some of the efforts ongoing within the FDA by the *In Vivo/In Vitro* Correlation Working Group for Extended Release Products to study all aspects of *in vivo/in vitro* correlations and produce guidances. There are currently sub-working groups addressing development, validation, and application. The de-

velopment sub-group is attempting to establish a mathematical model that describes the relationship between *in vitro* dissolution/release and a relevant *in vivo* response and is looking at the levels of correlation and methods of developing them. The validation sub-group is addressing what constitutes adequate experimental validation for a correlation, what data are required, and what methods are appropriate. The application sub-group is studying the use of a validated correlation for setting dissolution specifications in place of bioequivalency testing for certain manufacturing site changes.

During the breaks on the first day, samples of different dissolution apparatuses were on display and participants engaged in lively discussion with the vendors.

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